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 TITLE: VALDECOXIB COMPOSITIONS
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 DATE: July 19, 2002

CERTIFICATE OF MAILING

I hereby certify that this communication and recited enclosures are being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, DC 20231 on

July 19, 2002

Susan B. Howlitz

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

LETTER

On April 10, 2002, Applicant submitted a paper containing an Amendment and Response to Office Action in the above identified application. Referenced in that paper was Ecuador Patent Application No. 98-2761 (EC 98-2761). Applicant enclosed therewith a document having the running header "C-3169", which Applicant believed was an English language version of EC 98-2761. A separate copy of this same document was included with a Supplemental IDS submitted on April 11, 2002, and identified therein as Document B1.

It has just been learned by the undersigned that the "C-3169" document, submitted as Document B1, is not, as previously believed, an exact English language version of EC 98-2761. Applicant regrets this error, which was inadvertent and without deceptive intent.

Now enclosed herewith is a document having the running header "SRL 6098 PATENT", which is an exact English language version of EC 98-2761. The disclosure of this document is substantially similar, but not identical, to that of the previously submitted "C-3169" document. For instance, Example 18 of the "C-3169" document has no counterpart in EC 98-2761 ("SRL 6098 PATENT") as supplied herewith.

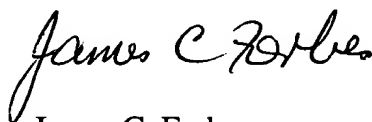
Applicant's paper of April 10, 2002 contains the following two paragraphs referring to various page and line numbers in EC 98-2761. These should be corrected as follows, in reference to the document supplied herewith:

EC 98-2761 teaches that celecoxib is preferably formulated in a dosage amount of about 50 mg to about 800 mg, more preferably about 75 mg to about 400 mg, and still more preferably about 100 mg to about 200 mg (EC 98-2761, [page 14 lines 22–24] page 8 lines 7–10). The present valdecoxib compositions are formulated in a much lower dosage amount, about 5 mg to about 40 mg as recited in Claim 1 as amended herein.

Furthermore, EC 98-2761 discloses celecoxib pharmacokinetic studies in adult human subjects wherein the amount of celecoxib administered was 300 mg (Example 13, see [page 58 lines 15–17] page 49 lines 4–6), 200 mg (Example 16, see [page 62 lines 2–5] page 53 lines 30–34), or 50 mg and 100 mg (Example 17, see [page 64 lines 7–11] page 56 lines 24–30), or 200 mg (Example 18, see page 67 lines 5–8)]. By contrast, as little as 20 mg valdecoxib in a composition of the present invention is disclosed in the present specification to provide a therapeutically effective concentration in blood serum within about 0.5 h after oral administration.

No fee is believed payable in connection with this communication. However, if it should be determined that a fee is payable, please charge such fee to Deposit Account No. 19-1025.

Respectfully submitted,



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Enclosures:
English language version of EC 98-2761, headed “SRL 6098 PATENT”



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SRL 6098
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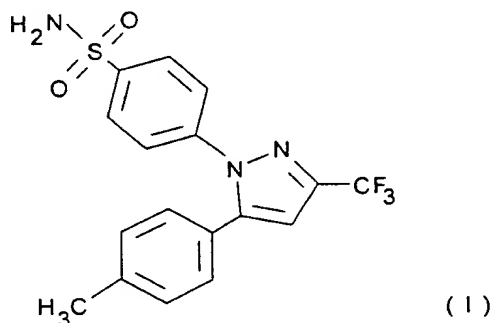
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CELECOXIB COMPOSITIONS**Field of the Invention**

The present invention relates to oral pharmaceutical compositions containing celecoxib as an active ingredient, methods of treatment comprising administering such oral pharmaceutical compositions to a subject in need thereof, and the use of such compositions in the manufacture of medicaments.

Background of the Invention

The compound 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide (also referred to herein as celecoxib) was previously reported in Talley et al., U.S. Patent 5,466,823 which describes and claims a class of 1,5-diaryl pyrazoles and their salts together with processes for the preparation of such compounds. Celecoxib has the structure:



The 1,5-diaryl pyrazole compounds reported in U.S. Patent 5,466,823 are described as useful in treating inflammation and inflammation-related disorders. U.S. Patent 5,466,823 contains general references to formulations for the administration of these 1,5-diaryl pyrazoles such as tablets and capsules.

Talley et al., U.S. Patent 5,760,068 reports a class of 1,5-diaryl pyrazole compounds including celecoxib that are described as selective inhibitors of cyclooxygenase-2 and that can be administered to treat, among other conditions and disorders, pathological conditions associated with rheumatoid arthritis and osteoarthritis.

Penning et al., "Synthesis and Biological Evaluation of the 1,5-Diarylpyrazole Class of Cyclooxygenase-2 Inhibitors: Identification of 4-[5-(4-Methylphenyl)-3-

(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide (SC-58635, Celecoxib)", J. Med.Chem. 40 (1997):1347-1365, discloses the preparation of a series of sulfonamide-containing 1,5-diarylpyrazole derivatives, including celecoxib, and the evaluation of those derivatives as cyclooxygenase-2 inhibitors.

5 Simon et al., "Preliminary Study of the Safety and Efficacy of SC-58635, a Novel Cyclooxygenase 2 Inhibitor", Arthritis & Rheumatism, Vol. 41, No. 9, September 1998, pp. 1591-1602, discloses a study of the efficacy and safety of celecoxib in the treatment of osteoarthritis and rheumatoid arthritis.

10 Lipsky et al., "Outcome of Specific COX-2 Inhibition in Rheumatoid Arthritis", J. Rheumatology, Vol. 24, Suppl. 49, pp. 9-14 (1997), discloses that in patients with rheumatoid arthritis the specific inhibition of cyclooxygenase-2 is sufficient to suppress signs and symptoms of inflammatory disease activity.

15 EP 863 134 A1 published September 9, 1998 discloses compositions comprising a cyclooxygenase-2 inhibitor, specifically 2-(3,5-difluorophenyl)-3-(4-methyl-sulfonyl)phenyl)-2-cyclopenten-1-one, in combination with microcrystalline cellulose, lactose monohydrate, hydroxypropyl cellulose, croscarmellose sodium and magnesium stearate.

Summary of the Invention

20 The effective administration of celecoxib to a subject has been complicated by the compound's low solubility and low compressibility as well as by its other physical and chemical properties. Pharmaceutical compositions comprising celecoxib and unique combinations of carrier materials, however, have been discovered that can effectively deliver a therapeutically preferred amount of the
25 compound to the subject when orally administered. These combinations of celecoxib and carrier materials have been found to possess improved bioavailability, chemical stability, physical stability, dissolution profiles, disintegration times, safety, and/or other improved pharmacokinetic, chemical and/or physical properties.

30 The present invention comprises these pharmaceutical compositions, unit dosage forms based thereon, and methods for the preparation and use of both. Other features of this invention will be in part apparent and in part pointed out hereinafter.

DETAILED DESCRIPTION OF THE INVENTION

Pharmaceutical compositions comprising celecoxib in a daily dosage amount from about 10 mg to about 1000 mg have been discovered that are unique compositions exhibiting improved performance as cyclooxygenase-2 inhibitors.

Such pharmaceutical compositions exhibit superior activity, potency, safety and/or therapeutic effectiveness at this dosage range for celecoxib. These compositions provide celecoxib to a patient at a dosage that is sufficient to provide prolonged inhibition of cyclooxygenase-2 and thus confer the desired therapeutic benefit while maintaining a safe clearance time for celecoxib. As discussed below, undesirable side-effects commonly observed for conventional non-steroidal antiinflammatory drugs also may be reduced or minimized with the pharmaceutical compositions of the present invention.

The compositions of the present invention would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other cyclooxygenase-2 mediated disorders, such as, as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compositions of the invention would be useful to treat arthritis, including but not limited to, rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such compositions of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, preterm labor, tendinitis, bursitis, allergic neuritis, cytomegalovirus infectivity, apoptosis including HIV induced apoptosis, lumbago, liver disease including hepatitis, skin-related conditions such as psoriasis, eczema, acne, UV damage, burns and dermatitis, and from post-operative inflammation including from ophthalmic surgery such as cataract surgery and refractive surgery. Compositions of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis. Compositions of the invention would be useful in treating inflammation in such diseases as migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, scleroderma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury including brain edema, myocardial ischemia, and the like. The compositions

would also be useful in the treatment of ophthalmic diseases, such as retinitis, conjunctivitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue. The compositions would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis, and in bone resorption such as associated with osteoporosis. The compositions would also be useful for the treatment of certain central nervous system disorders, such as cortical dementias including Alzheimer's disease, neurodegeneration, and central nervous system damage resulting from stroke, ischemia and trauma. The term "treatment" includes partial or total inhibition of the dementia, including Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, and senile dementia.

The compositions of the invention would be useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. These compositions would also be useful in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, and liver disease. The compositions would also be useful in the treatment of pain, but not limited to postoperative pain, dental pain, muscular pain, and pain resulting from cancer.

The compositions above would be useful for, but not limited to, treating and preventing inflammation-related cardiovascular disorders in a subject. The compositions would be useful for treatment and prevention of vascular diseases, coronary artery disease, aneurysm, vascular rejection, arteriosclerosis, atherosclerosis including cardiac transplant atherosclerosis, myocardial infarction, embolism, stroke, thrombosis, including venous thrombosis, angina including unstable angina, coronary plaque inflammation, bacterial-induced inflammation including Chlamydia-induced inflammation, viral induced inflammation, and inflammation associated with surgical procedures such as vascular grafting including coronary artery bypass surgery, revascularization procedures including angioplasty, stent placement, endarterectomy, or other invasive procedures involving arteries, veins and capillaries. The compositions would be useful for, but not limited to, the treatment of angiogenesis-related disorders in a subject. According to the present invention, the compositions can be administered to a subject in need of angiogenesis inhibition. The compositions would be useful for treatment of neoplasia, including metastasis; ophthalmological conditions such as corneal graft

on bleeding times including inhibition of platelet function, and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

These compositions would also be useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries following surgical and dental procedures. In addition, these compositions would inhibit cellular neoplastic transformations and metastatic tumour growth and hence can be used in the treatment of cancer, such as cancer of the colon. These compositions also would be of use in the treatment and/or prevention of cyclooxygenase-mediated proliferative disorders such as may occur in diabetic retinopathy and tumour angiogenesis.

These compositions also would inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence would be of use in the treatment of dysmenorrhea, premature labour, asthma and eosinophil related disorders. They also would be of use in the treatment of Alzheimer's disease, for decreasing bone loss particularly in postmenopausal women (i.e. treatment of osteoporosis), and for treatment of glaucoma.

By virtue of their high cyclooxygenase-2 (COX-2) activity and/or their specificity for cyclooxygenase-2 over cyclooxygenase-1 (COX-1), these compositions would be useful as an alternative to conventional non-steroidal antiinflammatory drugs (NSAID'S) particularly where such non-steroidal antiinflammatory drugs may be contraindicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; gastrointestinal bleeding, coagulation disorders including anemia such as hypoprothrombinemia, hemophilia or other bleeding problems; kidney disease; or in patients prior to surgery or patients taking anticoagulants. A brief description of the potential utility of cyclooxygenase-2 inhibitors is given in an article by John Vane, Nature, Vol. 367, pp. 215-216, 1994, and in an article in Drug News and Perspectives, Vol. 7, pp. 501-512, 1994.

Preferred uses for the pharmaceutical compositions of the present invention are for the treatment of rheumatoid arthritis and osteoarthritis, for pain management

rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, macular degeneration, retrolental fibroplasia and neovascular glaucoma; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including invantile hemaginomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis.

The compositions of the invention would be useful for the prevention or treatment of benign and malignant tumors/neoplasia including cancer, such as colorectal cancer, brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophogeal cancer, small bowel cancer and stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamus cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. Preferably, neoplasia is selected from gastrointestinal cancer, Barrett's esophagus, liver cancer, bladder cancer, pancreas cancer, ovary cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamus cell and basal cell cancers. The compositions can also be used to treat the fibrosis which occurs with radiation therapy. The compositions can be used to treat subjects having adenomatous polyps, including those with familial adenomatous polyposis (FAP). Additionally, the compositions can be used to prevent polyps from forming in patients at risk of FAP.

The compositions of the present invention also would possess anti-inflammatory, antipyretic and analgesic properties similar to conventional non-steroidal anti-inflammatory drugs. These compositions also would inhibit hormone-induced uterine contractions and have potential anti-cancer effects, but with a diminished ability to induce some of the mechanism-based side effects. In particular, such compositions would have a reduced potential for gastrointestinal toxicity and gastrointestinal irritation including upper gastrointestinal ulceration and bleeding, a reduced potential for renal side effects such as reduction in renal function leading to fluid retention and exacerbation of hypertension, a reduced effect

generally (particularly post-oral surgery pain, post-general surgery pain, post-orthopedic surgery pain, and acute flares of osteoarthritis), the treatment of Alzheimer's disease, and colon cancer chemoprevention.

Besides being useful for human treatment, these compositions are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents and the like. More preferred animals include horses, dogs, and cats.

Unformulated celecoxib administered in capsule form is not well absorbed in the gastrointestinal tract. In addition, unformulated celecoxib typically is cohesive and fuses into a monolithic mass upon compression in a die. Accordingly, a need exists for suitable celecoxib dosage forms. The pharmaceutical compositions of the present invention provide these dosage forms and exhibit one or more superior properties relative to unformulated celecoxib and/or other compositions comprising celecoxib. These superior properties include, but are not limited to, one or more of the following:

- (1) improved bioavailability;
- (2) improved solubility of the pharmaceutical composition;
- (3) decreased disintegration times for oral dosage forms;
- (4) decreased dissolution times for oral dosage forms;
- (5) decreased tablet friability;
- (6) increased tablet hardness;
- (7) improved safety for oral dosage forms;
- (8) improved composition wettability;
- (9) improved celecoxib and/or granule particle size distribution;
- (10) improved composition compressibility;
- (11) improved composition flow properties;
- (12) improved chemical stability of the final oral dosage form;
- (13) improved physical stability of the final oral dosage form;
- (14) decreased tablet or capsule size;
- (15) improved blend uniformity;
- (16) improved dose uniformity;
- (17) improved control of weight variation during encapsulation and/or tableting;
- (18) increased granule density for wet granulated compositions;

- (19) reduced water requirements for wet granulation;
- (20) reduced wet granulation time; and/or
- (21) reduced drying time for wet granulated mixtures.

Celecoxib Dosage of Pharmaceutical Compositions

The pharmaceutical compositions of the present invention comprise celecoxib in a daily dosage amount from about 10 mg to about 1000 mg. Preferably, the pharmaceutical compositions comprise celecoxib in an amount of about 50 mg to about 800 mg, more preferably about 75 mg to about 400 mg, and still more preferably about 100 mg to about 200 mg.

Treatment of Specific Conditions and Disorders

The pharmaceutical compositions of the present invention are useful where administration of a cyclooxygenase-2 inhibitor is indicated. It has been found that these compositions are particularly effective in the treatment of, for example, rheumatoid arthritis and osteoarthritis, and for pain management generally (particularly post-oral surgery pain, post-general surgery pain, post-orthopedic surgery pain, and acute flares of osteoarthritis), the treatment of Alzheimer's disease, and colon cancer chemoprevention.

For the treatment of rheumatoid arthritis, the pharmaceutical compositions provide a daily dosage of celecoxib in an amount of about 50 mg to about 1000 mg, preferably about 100 mg to about 600 mg, more preferably about 150 mg to about 500 mg, still more preferably about 175 to about 400, and still more preferably about 200 mg. A daily dose of about 0.67 to about 13.3 mg/kg body weight, preferably between about 1.33 and about 8.00 mg/kg body weight, more preferably between about 2.00 to about 6.67 mg/kg body weight, still more preferably between about 2.33 and about 5.33 mg/kg body weight, and still more preferably between about 2.67 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day, preferably one or two doses per day. Administration of a 100 mg unit oral dosage form twice-a-day is preferred for most patients, but some patients may benefit from administration of a 200 mg unit oral dosage form twice-a-day.

For the treatment of osteoarthritis, the pharmaceutical compositions provide a daily dosage of celecoxib in an amount of about 50 mg to about 1000 mg, preferably

about 100 mg to about 600 mg, more preferably about 150 mg to about 500 mg, still more preferably about 175 to about 400, and still more preferably about 200 mg. A daily dose of about 0.67 to about 13.3 mg/kg body weight, preferably between about 1.33 and about 8.00 mg/kg body weight, more preferably between about 2.00 to about 6.67 mg/kg body weight, still more preferably between about 2.33 and about 5.33 mg/kg body weight, and still more preferably between about 2.67 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day, preferably one or two doses per day. Administration of a 100 mg unit oral dosage form twice-a-day or a 200 mg unit oral dosage form once-a-day is preferred.

For the treatment of Alzheimer's disease, the pharmaceutical composition provides a daily dosage of celecoxib in an amount of about 50 mg to about 1000 mg, preferably about 100 mg to about 800 mg, more preferably about 150 mg to about 600 mg, still more preferably about 175 to about 400, and still more preferably about 400 mg. A daily dose of about 0.67 to about 13.3 mg/kg body weight, preferably between about 1.33 and about 10.67 mg/kg body weight, more preferably between about 2.00 to about 8.00 mg/kg body weight, still more preferably between about 2.33 and about 5.33 mg/kg body weight, and still more preferably between about 5.33 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day, preferably one or two doses per day. Administration of a 200 mg unit oral dosage form twice-a-day is preferred for most patients.

For the treatment of cancer, the pharmaceutical composition provides a daily dosage of celecoxib in an amount of about 50 mg to about 1000 mg, preferably about 100 mg to about 800 mg, more preferably about 150 mg to about 600 mg, still more preferably about 175 to about 400, and still more preferably about 400 mg. A daily dose of about 0.67 to about 13.3 mg/kg body weight, preferably between about 1.33 and about 10.67 mg/kg body weight, more preferably between about 2.00 to about 8.00 mg/kg body weight, still more preferably between about 2.33 and about 5.33 mg/kg body weight, and still more preferably between about 5.33 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day, preferably two doses per day. Administration of a 200 mg unit oral dosage twice-a-day is preferred for most patients.

In general, the pharmaceutical composition preferably is suitable to provide an average blood serum concentration of celecoxib of at least about 100 ng/mL in a subject over a period of about 24 hours after ingestion of the composition by the subject.

5 It also has been found that the pharmaceutical compositions of the present invention provide a therapeutic effect as cyclooxygenase-inhibitors over an interval of about 12 to 24 hours, preferably about 24 hours, after oral administration.

Unit Dosages

10 Dosage unit forms of the pharmaceutical compositions may typically contain, for example, a 10, 20, 25, 37.5, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350 or 400 mg dose of celecoxib. Preferred dosage unit forms contain about 100 mg or about 200 mg of celecoxib. The dosage unit form may be selected to accommodate the desired frequency of administration used to achieve the specified daily dosage.

15 The amount of the unit dosage form of the pharmaceutical composition that is administered and the dosage regimen for treating the condition or disorder will depend on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the condition or disorder, the route and frequency of administration, and thus may vary widely.

20 It has been discovered, however, that a once-a-day or twice-a-day administration regimen to achieve the required daily dosage of the pharmaceutical compositions of the present invention exhibits improved efficacy relative to other administration regimens for the unit dosage forms described in the examples of this application. Accordingly, once-a-day or twice-a-day administration is preferred.

Preparation of Celecoxib

25 The celecoxib used in the novel pharmaceutical compositions of the present invention can be prepared in the manner set forth in Talley et al., U.S. Patent 5,466,823, or in Zhi et al., WO96/37476.

Form of Pharmaceutical Compositions

30 The pharmaceutical compositions of the present invention comprise celecoxib in association with one or more non-toxic, pharmaceutically-acceptable carriers, excipients and/or adjuvants (collectively referred to herein as "carrier materials")

suitable for administration orally. The carrier materials must be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the recipient. The pharmaceutical compositions of the present invention may be adapted for administration by any suitable oral route by selection of appropriate carrier materials and a dosage of celecoxib effective for the treatment intended. Accordingly, the carrier material employed can be a solid or a liquid, or both, and is preferably formulated as a unit-dose composition, for example, a capsule or tablet, which can contain from about 1% to about 95%, preferably about 10% to about 90%, more preferably about 25% to about 85%, and still more preferably about 30% to about 80%, by weight of celecoxib. Such pharmaceutical compositions of the invention can be prepared by any of the well known techniques of pharmacy, consisting essentially of admixing the components.

For oral administration, the pharmaceutical composition may contain a desired amount of celecoxib and be in the form of, for example, a tablet, a hard or soft capsule, a lozenge, a cachet, a dispensable powder, granules, a suspension, an elixir, a liquid, or any other form reasonably adapted for oral administration. Such a pharmaceutical composition is preferably made in the form of a discrete dosage unit containing a predetermined amount of celecoxib, such as tablets or capsules. Such oral dosage forms may further comprise, for example, buffering agents. Tablets, pills and the like additionally can be prepared with or without coatings.

Pharmaceutical compositions suitable for buccal (sub-lingual) administration include, for example, lozenges comprising celecoxib in a flavored base, such as sucrose, and acacia or tragacanth, and pastilles comprising celecoxib in an inert base such as gelatin and glycerin or sucrose and acacia.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise, for example, wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

As indicated above, these pharmaceutical compositions can be prepared by any suitable method of pharmacy which includes the step of bringing into association the celecoxib and the carrier material or carrier materials. In general, the compositions are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary,

encapsulating or shaping the product. For example, a tablet can be prepared by compressing or molding a powder or granules of the compound, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binding agent, lubricant, inert diluent and/or surface active/dispersing agent(s). Molded tablets can be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

Carrier Materials

As noted above, the pharmaceutical compositions of the present invention comprise celecoxib in a therapeutically effective amount in combination with one or more pharmaceutically-acceptable carrier materials appropriate for oral administration. Oral dosage forms of the pharmaceutical compositions of the present invention preferably comprise celecoxib in a desired amount admixed with one or more carrier materials selected from the group consisting of pharmaceutically acceptable diluents, disintegrants, binding agents and adhesives, wetting agents, lubricants, anti-adherent agents and/or other carrier materials. More preferably, such compositions are tableted or encapsulated for convenient administration. Such capsules or tablets may be in the form of immediate release capsules or tablets.

The selection and combination of carrier materials used in the pharmaceutical compositions of the present invention provides compositions exhibiting improved performance with respect to, among other properties, efficacy, bioavailability, clearance times, stability, compatibility of celecoxib and carrier materials, safety, dissolution profile, disintegration profile and/or other pharmacokinetic, chemical and/or physical properties. The carrier materials preferably are water soluble or water dispersible and have wetting properties to offset the low aqueous solubility and hydrophobicity of celecoxib. Where the composition is formulated as a tablet, the combination of carrier materials selected provides tablets that may exhibit, among other properties, improved dissolution and disintegration profiles, hardness, crushing strength, and/or friability.

Diluents

The pharmaceutical compositions of the present invention optionally may comprise one or more pharmaceutically-acceptable diluents as a carrier material. Suitable diluents may include, either individually or in combination, such diluents as
5 lactose USP; lactose USP, anhydrous; lactose USP, spray dried; starch USP; directly compressible starch; mannitol USP; sorbitol; dextrose monohydrate; microcrystalline cellulose NF; dibasic calcium phosphate dihydrate NF; sucrose-based diluents; confectioner's sugar; monobasic calcium sulfate monohydrate; calcium sulfate dihydrate NF; calcium lactate trihydrate granular NF; dextrates, NF
10 (e.g., Emdex); Celutab; dextrose (e.g., Cerelease); inositol; hydrolyzed cereal solids such as the Maltrons and Mor-Rex; amylose; Rexcel; powdered cellulose (e.g., Elcema); calcium carbonate; glycine; bentonite; polyvinylpyrrolidone; and the like. The present pharmaceutical compositions comprise one or more diluents in the range of about 5% to about 99%, preferably about 10% to about 85%, and more
15 preferably about 20% to about 80%, of the total weight of the composition. The diluent or diluents selected preferably exhibit suitable flow properties and, where tablets are desired, compressibility.

Lactose and microcrystalline cellulose, either individually or in combination, are preferred diluents. Both diluents are chemically compatible with celecoxib. The
20 use of extragranular microcrystalline cellulose (that is, microcrystalline cellulose added to a wet granulated composition after the drying step) can be used to improve hardness (for tablets) and/or disintegration time. Lactose, especially lactose monohydrate, is particularly preferred. Lactose typically provides pharmaceutical compositions having suitable celecoxib release rates, stability, pre-compression
25 flowability, and/or drying properties at a relatively low diluent cost. It provides a high density substrate that aids densification of the granulation (where wet granulation is employed) and therefore improves blend flow properties.

Disintegrants

30 The pharmaceutical compositions of the present invention optionally may comprise one or more pharmaceutically-acceptable disintegrants as a carrier material, particularly for tablet formulations. Suitable disintegrants may include, either individually or in combination, such disintegrants as starches; sodium starch glycolate; clays (such as Veegum HV); celluloses (such as purified cellulose,

methycellulose and sodium carboxymethylcellulose, and carboxymethylcellulose); alginates; pregelatinized corn starches (such as National 1551 and National 1550); Croscopovidone, USP NF; gums (such as agar, guar, locust bean, Karaya, pectin, and tragacanth). Disintegrants may be added at any suitable step during the preparation of the pharmaceutical composition, particularly prior to granulation or during the lubrication step prior to compression. The present pharmaceutical compositions comprise one or more disintegrants in the range of about 0.2% to about 30%, preferably about 0.2% to about 10%, and more preferably about 0.2% to about 5%, of the total weight of the composition.

Croscarmellose sodium is a preferred disintegrant for tablet or capsule disintegration, preferably in the range of about 0.2% to about 10%, more preferably in the range of about 0.2% to about 6%, and still more preferably in the range of about 0.2% to about 5%, by weight of the composition. Croscarmellose sodium confers superior intragranular disintegration capabilities to the pharmaceutical composition of the present invention.

Binding Agents and Adhesives

The pharmaceutical compositions of the present invention optionally may comprise one or more pharmaceutically-acceptable binding agents or adhesives as a carrier material, particularly for tablet formulations. Such binding agents and adhesives preferably impart sufficient cohesion to the powders to allow for normal processing such as sizing, lubrication, compression and packaging, but still allow the tablet to disintegrate and the composition to dissolve upon ingestion. Suitable binding agents and adhesives may include, either individually or in combination, such binding agents and adhesives as acacia; tragacanth; sucrose; gelatin; glucose; starch; cellulose materials such as, but not limited to, methylcellulose and sodium carboxymethylcellulose (e.g., Tylose); alginic acid and salts of alginic acid; magnesium aluminum silicate; polyethylene glycol; guar gum; polysaccharide acids; bentonites; polyvinylpyrrolidone; polymethacrylates; hydroxypropylmethylcellulose (HPMC); hydroxypropylcellulose (Klucel); ethylcellulose (Ethocel); pregelatinized starch (such as National 1511 and Starch 1500). The present pharmaceutical compositions comprise one or more binding agents and/or adhesives in the range of about 0.5% to about 25%, preferably about 0.75% to about 15%, and more preferably about 1% to about 10%, of the total weight of the composition.

Polyvinylpyrrolidone is a preferred binding agent used impart cohesive properties to the powder blend of the celecoxib formulation. The compositions preferably comprise polyvinylpyrrolidone in a range of about 0.5% to about 10%, more preferably about 0.5% to about 7%, and still more preferably about 0.5% to about 5%. Polyvinylpyrrolidone viscosities up to about 20 cp may be used although viscosities of about 6 cp or lower are preferred, particularly about 3 cp or lower. Polyvinylpyrrolidone provides cohesiveness to the blend and facilitates the necessary binding to form granules during wet granulation. In fact, pharmaceutical compositions of the present invention comprising polyvinylpyrrolidone, particularly in a wet granulated form, exhibited improved bioavailability relative to other compositions.

Wetting Agents

Celecoxib is largely insoluble in aqueous solution. Accordingly, the pharmaceutical compositions of the present invention optionally may comprise one or more pharmaceutically-acceptable wetting agents as a carrier material. Such wetting agents preferably maintain celecoxib in solution and improve the relative bioavailability of the pharmaceutical composition. Suitable wetting agents may include, either individually or in combination, such wetting agents as oleic acid; glyceryl monostearate; sorbitan mono-oleate; sorbitan monolaurate; triethanolamine oleate; polyoxyethylene sorbitan mono-oleate; polyoxyethylene sorbitan monolaurate; sodium oleate; and sodium lauryl sulfate. Wetting agents that are anionic surfactants are preferred. The present pharmaceutical compositions comprise one or more wetting agents in the range of about 0.25% to about 15%, preferably about 0.4% to about 10%, and more preferably about 0.5% to about 5%, of the total weight of the composition.

Sodium lauryl sulfate is a preferred wetting agent. The compositions of the present invention preferably comprise sodium lauryl sulfate as the wetting agent in the range of about 0.25% to about 7%, more preferably about 0.4% to about 6%, and still more preferably about 0.5 to about 5%.

Lubricants

The pharmaceutical compositions of the present invention optionally may comprise one or more pharmaceutically-acceptable lubricants and/or glidants as a

carrier material. Suitable lubricants and/or glidants may include, either individually or in combination, such lubricants and/or glidants as glyceryl behapate (Compritol 888); stearates (magnesium, calcium, sodium); stearic acid; hydrogenated vegetable oils (e.g., Sterotex); talc; waxes; Stearowet; boric acid; sodium benzoate and sodium acetate; sodium fumarate; sodium chloride; DL-Leucine; polyethylene glycols (e.g., Carbowax 4000 and Carbowax 6000); sodium oleate; sodium benzoate; sodium acetate; sodium lauryl sulfate; and magnesium lauryl sulfate. The present pharmaceutical compositions comprise one or more lubricants in the range of about 0.1% to about 10%, preferably about 0.2% to about 8%, and more preferably about 0.25% to about 5%, of the total weight of the composition.

Magnesium stearate is a preferred lubricant used, for example, to reduce friction between the equipment and granulated mixture during compression for tablet formulations.

Other carrier materials (such as anti-adherent agents, colorants, flavors, sweeteners and preservatives) are known in the pharmaceutical art and can be used in the preparation of the pharmaceutical compositions of the present invention. For example, iron oxide can be added to the composition to provide a yellow color.

In one embodiment of the present invention, the pharmaceutical composition comprises celecoxib in a desired amount and a binding agent, preferably polyvinylpyrrolidone. The composition preferably further comprises one or more carrier materials selected from the group consisting of pharmaceutically acceptable diluents, disintegrants, binding agents, wetting agents, and lubricants. More preferably, the composition comprises one or more carrier materials selected from the group consisting of lactose, sodium lauryl sulfate, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. Still more preferably, the composition comprises lactose monohydrate and croscarmellose sodium. Still more preferably, the composition further comprises one or more of the carrier materials sodium lauryl sulfate, magnesium stearate, and microcrystalline cellulose.

In another embodiment, the pharmaceutical composition comprises:
about 1 to about 95 weight percent of celecoxib;
about 5 to about 99 weight percent of a pharmaceutically acceptably diluent;

about 0.5 to about 30 weight percent of a pharmaceutically acceptably disintegrant; and

about 0.5 to about 25 weight percent of a pharmaceutically acceptably binding agent.

5 In addition, this pharmaceutical composition may optionally comprise about 0.25 to about 15 weight percent of a pharmaceutically acceptably wetting agent; and/or about 0.1 to about 10 weight percent of a pharmaceutically acceptably lubricant. The term "weight percent" as used herein means the weight percent of a specified ingredient based upon the total weight of all ingredients of the composition.

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In another embodiment, the pharmaceutical composition comprises:

about 1 to about 95 weight percent of celecoxib;

about 5 to about 99 weight percent of lactose;

about 2 to about 6 weight percent of croscarmellose sodium; and

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about 0.5 to about 10 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 0.25 to about 7 weight percent of sodium lauryl sulfate; about 0.1 to about 10 weight percent of magnesium stearate; and/or about 1 to about 99 weight percent of microcrystalline cellulose.

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In another embodiment, the pharmaceutical composition comprises:

about 80 to about 220 mg of celecoxib;

about 30 to about 225 mg of lactose;

about 0.5 to about 25 mg of croscarmellose sodium; and

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about 0.5 to about 25 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 0.5 to about 25 mg of sodium lauryl sulfate; about 0.2 to about 10 mg of magnesium stearate; and/or about 1 mg to about 70 mg of microcrystalline cellulose.

30

In still another embodiment, the pharmaceutical composition is in the form of a unit dosage tablet or capsule.

In still another embodiment, the pharmaceutical composition comprises celecoxib and a carrier material or carrier materials in the form of an oral unit dosage

suitable for once-a-day or twice-a-day oral administration. Still more preferably, this pharmaceutical composition comprises celecoxib in a desired amount and a binding agent, preferably polyvinylpyrrolidone. The composition preferably further comprises one or more carrier materials selected from the group consisting of pharmaceutically acceptable diluents, disintegrants, binding agents, wetting agents, lubricants and anti-adherent agents. More preferably, the composition comprises one or more carrier materials selected from the group consisting of lactose, sodium lauryl sulfate, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. Still more preferably, the composition comprises lactose monohydrate and croscarmellose sodium. Still more preferably, the composition further comprises one or more of the carrier materials sodium lauryl sulfate, magnesium stearate, and microcrystalline cellulose. It is particularly preferred that the various components of the composition be present in the amounts or the weight fractions later disclosed in this application.

In still another embodiment, the pharmaceutical composition comprises celecoxib and a pharmaceutically acceptable carrier material or carrier materials that when orally administered to a human patient in need thereof provides a therapeutic effect as a cyclooxygenase-2 inhibitor over an interval of about 12 to about 24 hours, preferably at least about 24 hours, after oral administration. Still more preferably, this pharmaceutical composition comprises celecoxib in a desired amount and a binding agent, preferably polyvinylpyrrolidone. The composition preferably further comprises one or more carrier materials selected from the group consisting of pharmaceutically acceptable diluents, disintegrants, binding agents, wetting agents, lubricants and anti-adherent agents. More preferably, the composition comprises one or more carrier materials selected from the group consisting of lactose, sodium lauryl sulfate, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. Still more preferably, the composition comprises lactose monohydrate and croscarmellose sodium. Still more preferably, the composition further comprises one or more of the carrier materials sodium lauryl sulfate, magnesium stearate, and microcrystalline cellulose. It is particularly preferred that the various components of the composition be present in the amounts or the weight fractions later disclosed in this application.

Tablets and Capsules

The pharmaceutical compositions of the present invention preferably are tablets, capsules or the like, and more preferably are in the form of immediate release tablets or capsules. These pharmaceutical compositions comprise celecoxib in an appropriate unit dosage of celecoxib sufficient to provide the required daily dosage, that is, such as tablets or capsules orally administered in accordance with a predetermined regimen provide a total daily dosage of about 10 mg to about 1000 mg, more preferably about 50 mg to about 800 mg, still more preferably about 75 mg to about 400 mg, and still more preferably about 100 mg to about 200 mg, of celecoxib. While the amount of celecoxib in such novel compositions preferably is within the ranges previously discussed, the formulations also may be useful for the administration of an amount of celecoxib falling outside of the disclosed dosage ranges.

Celecoxib Particle Size

While the pharmaceutical compositions are effective for broad range of particle sizes for the initial celecoxib starting material used in the compositions, it has been discovered that reduction of the particle size can improve celecoxib bioavailability. Accordingly, the D_{90} particle size (that is, the particle size of at least 90% of the particles) of the celecoxib used as a starting material in the composition preferably is less than about 200 microns, more preferably less than about 100 microns, still more preferably less than about 75 microns, and still more preferably less than 40 microns. For example, as illustrated in Example 11, reducing the D_{90} particle size of the starting material celecoxib from about 60 microns to about 30 microns can materially improve the bioavailability of the pharmaceutical composition.

Granulation Particle Size and Flow Properties

While the pharmaceutical compositions of the present invention may be prepared, for example, by direct encapsulation or direct compression, they preferably are wet granulated prior to encapsulation or compression. Wet granulation, among other matters, densifies the compositions resulting in improved flow properties, improved compression characteristics and easier metering or weight dispensing of the final compositions. The particle size of the granulation is not narrowly critical, the important parameters being that the average particle size of the

granules preferably allows for convenient handling and processing and, for tablets, permits the formation of a directly compressible mixture that forms pharmaceutically acceptable tablets.

The desired tap and bulk densities of the granulation are normally between about 0.3 g/ml to about 1.0 g/ml.

Dissolution Profile

The compositions of the present invention preferably are immediate release compositions that release at least about 50% of the celecoxib in vitro within about 15 minutes of ingestion. More preferably, they release at least about 60% of the celecoxib in vitro within about 30 minutes of ingestion. Still more preferably, they release at least about 75% of the celecoxib in vitro within about 45 minutes of ingestion.

Disintegration Profile

Carrier materials for immediate release compositions preferably are selected to provide a disintegration time less than about 30 minutes, preferably about 25 minutes or less, more preferably about 20 minutes or less, and still more preferably about 15 minutes or less.

Hardness

For tablet formulations, the complete mixture in an amount sufficient to make a uniform batch of tablets is subjected to tableting in a conventional production scale tableting machine at normal compression pressure (for example, about 1 KN to about 50 KN). Any tablet hardness convenient with respect to handling, manufacture, storage and ingestion may be employed. For 100 mg tablets, hardness is preferably at least 4 kp, more preferably at least about 5 kp, and still more preferably at least about 6 kp. For 200 mg tablets, hardness is preferably at least 7 kp, more preferably at least about 9 kp, and still more preferably at least about 11. The mixture, however, is not be compressed to such a degree that there is subsequent difficulty in achieving hydration when exposed to gastric fluid.

Friability

For tablet formulations, tablet friability preferably is less than about 1.0%, more preferably less than 0.8%, and still more preferably less than about 0.5%.

In another embodiment, the pharmaceutical composition comprises:

5 about 25 to about 85 weight percent of celecoxib;
 about 5 to about 70 weight percent of lactose; —
 about 0.5 to about 7 weight percent of polyvinylpyrrolidone; and
 about 0.2 to about 5 weight percent of croscarmellose sodium.

10 In addition, this pharmaceutical composition may optionally comprise about 0.4 to
 about 6 weight percent of sodium lauryl sulfate; about 0.2 to about 8 weight percent
 of magnesium stearate; and/or about 0.1 to about 15 weight percent of
 microcrystalline cellulose. The composition preferably is in the form of a unit dosage
 capsule.

15 In another embodiment, the pharmaceutical composition comprises:
 about 27 to about 47 weight percent of celecoxib;
 about 45 to about 65 weight percent of lactose;
 about 0.5 to about 5 weight percent of croscarmellose sodium; and
 about 0.5 to about 5 weight percent of polyvinylpyrrolidone.

20 In addition, this pharmaceutical composition may optionally comprise about 0.25 to
 about 7 weight percent of sodium lauryl sulfate; and/or about 0.25 to about 5 weight
 percent of magnesium stearate. The composition preferably is in the form of a unit
 dosage capsule.

25 In this embodiment, the pharmaceutical composition preferably comprises:
 about 32 to about 42 weight percent of celecoxib;
 about 50 to about 60 weight percent of lactose;
 about 0.5 to about 3 weight percent of croscarmellose sodium; and
 about 1 to about 5 weight percent of polyvinylpyrrolidone.

30 In addition, this pharmaceutical composition may optionally comprise about 0.4 to
 about 6 weight percent of sodium lauryl sulfate; and/or about 0.5 to about 3 weight
 percent of magnesium stearate.

In this embodiment, the pharmaceutical composition preferably comprises:

about 35 to about 39 weight percent of celecoxib;
about 54 to about 57 weight percent of lactose;
about 0.5 to about 2 weight percent of croscarmellose sodium; and
about 1.5 to about 4.5 weight percent of polyvinylpyrrolidone.

5 In addition, this pharmaceutical composition may optionally comprise about 2 to about 4 weight percent of sodium lauryl sulfate; and/or about 0.5 to about 2 weight percent of magnesium stearate.

10 In another embodiment, the pharmaceutical composition comprises:
about 65 to about 85 weight percent of celecoxib;
about 8 to about 28 weight percent of lactose;
about 0.5 to about 5 weight percent of croscarmellose sodium; and
about 0.5 to about 5 weight percent of polyvinylpyrrolidone.

15 In addition, this pharmaceutical composition may optionally comprise about 0.25 to about 7 weight percent of sodium lauryl sulfate; and/or about 0.25 to about 5 weight percent of magnesium stearate. The composition preferably is in the form of a unit dosage capsule.

20 In this embodiment, the pharmaceutical composition preferably comprises:
about 69 to about 79 weight percent of celecoxib;
about 13.5 to about 23.5 weight percent of lactose;
about 0.5 to about 3 weight percent of croscarmellose sodium; and
about 1 to about 5 weight percent of polyvinylpyrrolidone.

25 In addition, this pharmaceutical composition may optionally comprise about 0.4 to about 6 weight percent of sodium lauryl sulfate; and/or about 0.5 to about 3 weight percent of magnesium stearate.

30 In this embodiment, the pharmaceutical composition preferably comprises:
about 72 to about 76 weight percent of celecoxib;
about 16.5 to about 20.5 weight percent of lactose;
about 0.5 to about 2 weight percent of croscarmellose sodium; and
about 1.5 to about 4.5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 2 to about 4 weight percent of sodium lauryl sulfate; and/or about 0.5 to about 2 weight percent of magnesium stearate.

5 In another embodiment, the pharmaceutical composition comprises:
 about 30 to about 50 weight percent of celecoxib;
 about 30 to about 50 weight percent of lactose;
 about 0.5 to about 6 weight percent of croscarmellose sodium; and
 about 0.5 to about 5 weight percent of polyvinylpyrrolidone.

10 In addition, this pharmaceutical composition may optionally comprise about 1 to about 20 weight percent of microcrystalline cellulose; about 0.25 to about 7 weight percent of sodium lauryl sulfate; and/or about 0.25 to about 5 weight percent of magnesium stearate. The composition preferably is in the form of a unit dosage tablet.

15 In this embodiment, the pharmaceutical composition preferably comprises:
 about 35 to about 45 weight percent of celecoxib;
 about 35 to about 45 weight percent of lactose;
 about 1 to about 5 weight percent of croscarmellose sodium; and
20 about 1 to about 5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 5 to about 15 weight percent of microcrystalline cellulose; about 0.4 to about 6 weight percent of sodium lauryl sulfate; and/or about 0.5 to about 3 weight percent of magnesium stearate.

25 In this embodiment, the pharmaceutical composition preferably comprises:
 about 38 to about 42 weight percent of celecoxib;
 about 38 to about 42 weight percent of lactose;
 about 1.5 to about 4.5 weight percent of croscarmellose sodium; and
30 about 1.5 to about 4.5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 8 to about 12 weight percent of microcrystalline cellulose; about 2 to about 4 weight percent of sodium lauryl sulfate; and/or about 0.5 to about 2 weight percent of magnesium stearate.

In another embodiment, the pharmaceutical composition comprises:

about 95 to about 105 mg of celecoxib;

about 145 to about 155 mg of lactose monohydrate;

about 0.5 to about 8 mg of croscarmellose sodium; and

about 2 to about 12 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 3 to about 13 mg of sodium lauryl sulfate; and/or about 0.5 to about 8 mg of magnesium stearate. The composition preferably is in the form of a unit dosage capsule.

In this embodiment, the pharmaceutical composition preferably comprises:

about 98 to about 102 mg of celecoxib;

about 148 to about 152 mg of lactose monohydrate;

about 1.5 to about 4.5 mg of croscarmellose sodium; and

about 4.5 to about 8.5 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 6 to about 10 mg of sodium lauryl sulfate; and/or about 1 to about 5 mg of magnesium stearate.

In another embodiment, the pharmaceutical composition comprises:

about 195 to about 205 mg of celecoxib;

about 45 to about 55 mg of lactose monohydrate;

about 0.5 to about 8 mg of croscarmellose sodium; and

about 2 to about 12 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 3 to about 13 mg of sodium lauryl sulfate; and/or about 0.5 to about 8 mg of magnesium stearate. The composition preferably is in the form of a unit dosage capsule.

In this embodiment, the pharmaceutical composition preferably comprises:

about 198 to about 202 mg of celecoxib;

about 48 to about 52 mg of lactose monohydrate;

about 1.5 to about 4.5 mg of croscarmellose sodium; and

about 4.5 to about 8.5 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition may optionally comprise about 6 to about 10 mg of sodium lauryl sulfate; and/or about 1 to about 5 mg of magnesium stearate.

5 In another embodiment, the pharmaceutical composition comprises:
 about 95 to about 105 mg of celecoxib;
 about 92 to about 112 mg of lactose monohydrate;
 about 2 to about 13 mg of croscarmellose sodium; and
 about 1 to about 11 mg of polyvinylpyrrolidone.

10 In addition, this pharmaceutical composition may optionally comprise about 20 to about 30 mg of microcrystalline cellulose; about 3 to about 13 mg of sodium lauryl sulfate; and/or about 0.5 to about 7 mg of magnesium stearate. The composition preferably is in the form of a unit dosage tablet.

15 In this embodiment, the pharmaceutical composition preferably comprises:
 about 98 to about 102 mg of celecoxib;
 about 100 to about 104 mg of lactose monohydrate;
 about 5 to about 10 mg of croscarmellose sodium; and
 about 4 to about 8.5 mg of polyvinylpyrrolidone.

20 In addition, this pharmaceutical composition may optionally comprise about 23 to about 27 mg of microcrystalline cellulose; about 5 to about 10 mg of sodium lauryl sulfate; and/or about 0.5 to about 4 mg of magnesium stearate.

25 In another embodiment, the pharmaceutical composition comprises:
 about 195 to about 205 mg of celecoxib;
 about 199 to about 209 mg of lactose monohydrate;
 about 10 to about 20 mg of croscarmellose sodium; and
 about 7.5 to about 17.5 mg of polyvinylpyrrolidone.

30 In addition, this pharmaceutical composition may optionally comprise about 45 to about 55 mg of microcrystalline cellulose; about 10 to about 20 mg of sodium lauryl sulfate; and/or about 0.5 to about 9 mg of magnesium stearate. The composition preferably is in the form of a unit dosage tablet.

In this embodiment, the pharmaceutical composition preferably comprises:

about 98 to about 102 mg of celecoxib;
about 202 to about 206 mg of lactose monohydrate;
about 13 to about 17 mg of croscarmellose sodium; and
about 10.5 to about 14.5 mg of polyvinylpyrrolidone.

5 In addition, this pharmaceutical composition may optionally comprise about 48 to about 52 mg of microcrystalline-cellulose; about 13 to about 17 mg of sodium lauryl sulfate; and/or about 2 to about 6 mg of magnesium stearate.

10 In still another embodiment, the pharmaceutical composition is capable of releasing in vitro at least 50% of the celecoxib contained in the composition within about 15 minutes of ingestion of the composition.

15 In still another embodiment, the present invention comprises the pharmaceutical compositions described above in unit dosage form.

20 In still another embodiment, the present invention comprises the pharmaceutical compositions described above in unit dosage form suitable for once-a-day or twice-a-day administration.

25 In still another embodiment, the present invention comprises the pharmaceutical compositions described above in immediate release unit dosage form, preferably a tablet or a capsule.

30 In still another embodiment, the pharmaceutical composition comprises celecoxib wherein the composition is an immediate release oral dosage form, preferably a tablet or capsule, that releases in vitro at least about 50%, preferably at least about 60%, and more preferably at least about 75%, of the celecoxib contained in the composition within about 45 minutes of ingestion by a subject. Preferably, the composition further comprises one or more pharmaceutically acceptable carrier materials selected from the group consisting of lactose, polyvinylpyrrolidone, croscarmellose sodium, sodium lauryl sulfate, magnesium stearate, and microcrystalline cellulose. It is particularly preferred that the various components of the composition be present in the amounts or the weight fractions set forth above.

In still another embodiment, the pharmaceutical composition comprises celecoxib and a pharmaceutically acceptable carrier material or carrier materials wherein the composition when orally administered to a human patient in need thereof provides a therapeutic effect as a cyclooxygenase-2 inhibitor over an interval of about 12 to about 24 hours, preferably at least about 24 hours, after oral administration. Still more preferably, this pharmaceutical composition comprises celecoxib, and one or more carrier materials selected from the group consisting of lactose, polyvinylpyrrolidone, croscarmellose sodium, sodium lauryl sulfate, magnesium stearate, and microcrystalline cellulose. It is particularly preferred that the various components of the composition be present in the amounts or the weight fractions set forth above.

In still another embodiment, the pharmaceutical composition comprises celecoxib and a pharmaceutically acceptable carrier material or carrier materials in the form of an immediate release oral dosage tablet or capsule suitable for once-a-day or twice-a-day oral administration. Still more preferably, this pharmaceutical composition comprises celecoxib and one or more carrier materials selected from the group consisting of lactose, polyvinylpyrrolidone, croscarmellose sodium, sodium lauryl sulfate, magnesium stearate, and microcrystalline cellulose. It is particularly preferred that the various components of the composition be present in the amounts or the weight fractions set forth above.

Method of Treatment

The present invention also is directed to a therapeutic method of treating a condition or disorder where treatment with a cyclooxygenase-2 inhibitor is indicated, the method comprising the oral administration of one or more of the pharmaceutical compositions of the present invention to a patient in need thereof. The dosage regimen to prevent, give relief from, or ameliorate the condition or disorder preferably corresponds to the once or twice a day oral dosages discussed above, but may be modified in accordance with a variety of factors. These include the type, age, weight, sex, diet, and medical condition of the patient and the severity of the disease. Thus, the dosage regimen actually employed may vary widely and therefore deviate from the preferred dosage regimen set forth above.

Initial treatment of a patient suffering from a condition or disorder where treatment with a cyclooxygenase-2 inhibitor is indicated can begin with the dosages indicated above. Treatment is generally continued as necessary over a period of several weeks to several months or years until the condition or disorder has been controlled or eliminated. Patients undergoing treatment with the compositions disclosed herein can be routinely monitored by any of the methods well known in the art to determine the effectiveness of therapy. Continuous analysis of such data permits modification of the treatment regimen during therapy so that optimal effective amounts of compounds of the present invention are administered at any point in time, and so that the duration of treatment can be determined as well. In this way, the treatment regimen/dosing schedule can be rationally modified over the course of therapy so that the lowest amount of celecoxib exhibiting satisfactory effectiveness is administered, and so that administration is continued only so long as is necessary to successfully treat the condition or disorder.

Method For Preparation Of Formulation

The present invention also is directed to methods for the preparation of pharmaceutical compositions comprising celecoxib. In particular, the present invention is directed to methods for the preparation of pharmaceutical compositions comprising celecoxib in unit dosage form, particularly in tablet or capsule unit dosage form, such that each unit dosage form includes an amount of celecoxib sufficient to provide a therapeutic effect for about 12 to 24 hours. Each unit dosage form preferably contains, for example, from about 100 mg to about 200 mg of celecoxib. Where tablets or capsules are desired, wet granulation, dry granulation or direct compression or encapsulation methods can be employed.

Wet granulation is the preferred method of preparing the pharmaceutical compositions of the present invention. In the wet granulation process, the celecoxib (and, if desired, any of the other carrier materials) is initially milled or micronized to the desired particle size using a conventional mill or grinder. As previously discussed, reduction of the D_{90} particle size to less than about 200 microns, preferably less than about 100 microns, more preferably less than about 75 microns, and still more preferably less than about 40 microns, can materially increase the bioavailability of the celecoxib.

The milled or micronized celecoxib is then blended, for example in a high shear mixer granulator, planetary mixer, a twin-shell blender or sigma mixer, with one or more of the carrier materials. Typically, the drug is blended with the diluent(s), disintegrant(s), binding agent(s) and, optionally, wetting agent(s) in this step although it may be possible to add all or a portion of one or more of the carrier materials in a later step. For example, in tablet formulations where croscarmellose sodium is employed as a diluent, it has been discovered that addition of a portion of the croscarmellose sodium during this blending step (intragranular croscarmellose sodium) and the addition of the remaining portion after the drying step discussed below (extragranular croscarmellose sodium) can increase the hardness and/or decrease the friability of the tablets produced. In this situation, preferably about 60% to about 75% of the croscarmellose sodium is added intragranularly and about 25% to about 40% of the croscarmellose sodium is added extragranularly. Similarly, for tablet formulations it has been discovered that addition of microcrystalline cellulose after the drying step below (extragranular microcrystalline cellulose) can improve compressibility of the granulation and hardness of the tablets prepared from the granulation. This blending step of the process preferably comprises the blending of celecoxib, lactose, polyvinylpyrrolidone and croscarmellose sodium. It has been discovered that blending times as short as three minutes can provide a dry powder mixture having a sufficiently uniform distribution of celecoxib. For example, the dry powder mixtures used in the preparation of 100 mg dose capsules (1080 kg total batch size) and 200 mg dose capsules (918 kg total batch size), respectively, had measured relative standard deviation values of 3.6% or less and 1.1% or less, respectively.

Water is then added to the dry powder mixture and the mixture is blended for an additional period of time. The wetting agent used preferably is first combined with the water and mixed for at least 15 minutes, preferably at least 20 minutes, prior to adding the water to the dry powder mixture. The water can be added to the mixture at once, gradually over a period of time, or in several portions over a period of time. The water preferably is added gradually over a period of time.

For the illustrative 100 mg dose capsules (1080 kg batch), for example, water addition rates between about 5 to about 25 kg/minute, preferably about 7 to about 20 kg/minute, and still more preferably about 8 to about 18 kg/minute, provide suitable results. An additional period of mixing after the water addition is complete is

preferred to ensure the uniform distribution of the water in the mixture. For this batch additional mixing times of about 2 to about 10 minutes, preferably about 3 to about 9 minutes, and more preferably about 3 to about 7 minutes, provide suitable results. The wet granulated mixture of this batch preferably comprises about 2% to about 15% water by weight, more preferably about 4% to about 12%, and still more preferably about 6% to about 10%.

For the illustrative 200 mg dose capsules (918 kg batch), for example, water addition rates between about 5 to about 25 kg/minute, preferably about 7 to about 23 kg/minute, and still more preferably about 8 to about 21 kg/minute, provide suitable results. An additional period of mixing after the water addition is complete is preferred to ensure the uniform distribution of the water in the mixture. For this batch additional mixing times of about 2 to about 15 minutes, preferably about 3 to about 12 minutes, and more preferably about 3 to about 10 minutes, provide suitable results. The wet granulated mixture of this batch preferably comprises about 2% to about 15% water by weight, more preferably about 6% to about 14%, and still more preferably about 8% to about 13%.

The wet granulated mixture preferably is then wet milled, for example with a screening mill, to eliminate large material agglomerations that form as a by-product of the wet granulation operation. If not removed, these agglomerations would prolong the subsequent fluidized bed drying operation and increase the variation with respect to moisture control. For the illustrative 100 mg dose capsules (1080 kg batch) and 200 mg dose capsules (918 kg batch), for example, suitable granulations can be obtained using feed rates up to about 50%, preferably about 2% to about 30%, and still more preferably about 5% to about 20%; and screen sizes of about 1 inch.

The wet granulated/wet milled mixture is then dried, for example, in an oven or a fluidized bed dryer, preferably a fluidized bed drier. If desired, the wet granulated mixture can be extruded or spheronized prior to drying. For the drying process, conditions such as inlet air temperature and drying time are adjusted to achieve the desired moisture content for the dried mixture. It may be desirable to combine two or more granulation sections for this drying step and subsequent processing steps.

For the illustrative 100 mg dose capsules (1080 kg batch) discussed above, dryer inlet temperature can be fixed at 60°C although other inlet temperatures can

be used, preferably in the range of about 50°C to about 70°C. Air flow rate can be varied between about 1000 to about 8000 cubic feet per minute, preferably about 2000 to about 7000 cubic feet per minute, and still more preferably about 4000 to about 7000 cubic feet per minute, with a damper opening of about 10% to about 90%, preferably about 20% to about 80%, and still more preferably about 30% to about 70%. Dryer loads of about 35% to about 100%, preferably about 50% to about 100%, and still more preferably about 90% to about 100%, can be used. Average loss on drying under these conditions generally will be between about 0.1% to about 2.0%.

For the illustrative 200 mg dose capsules (918 kg batch) discussed above, dryer inlet temperature can be fixed at 60°C although other inlet temperatures can be used, preferably in the range of about 50°C to about 70°C. Air flow rate can be varied between about 1000 to about 8000 cubic feet per minute, preferably about 3000 to about 7000 cubic feet per minute, and still more preferably about 4000 to about 7000 cubic feet per minute, with a damper opening of about 10% to about 90%, preferably about 20% to about 80%, and still more preferably about 30% to about 70%. Dryer loads of about 35% to about 100%, preferably about 50% to about 100%, and still more preferably about 90% to about 100%, can be used. Average loss on drying under these conditions generally will be between about 0.1% to about 2.0%.

To the extent necessary, the dry granules are then reduced in size in preparation for compression. Conventional particle size reduction equipment such as oscillators or fitz mills can be employed. For the illustrative 100 mg dose capsules (1080 kg batch), for example, suitable granulations can be obtained using feed rates of about 20% to about 70%, preferably about 30% to about 60%; mill speeds of about 20% to about 70%, preferably about 40% to about 60%; and screen sizes of about 0.020 inch to about 0.070 inch, preferably about 0.028 inch to about 0.040 inch. For the illustrative 200 mg dose capsules (918 kg batch), for example, suitable granulations can be obtained using feed rates of about 10% to about 70%, preferably about 20% to about 60%; mill speeds of about 20% to about 60%, preferably about 30% to about 50%; and screen sizes of about 0.020 inch to about 0.080 inch, preferably about 0.028 inch to about 0.063 inch. Smaller screen sizes such as 0.028 inch, however, were observed to result in lower throughput of product. Larger screen sizes such as 0.063 inch, however, resulted in an increased

population of granules larger in size than 850 microns. Screen sizes around about 0.040 inch appear to eliminate an excessive population of granules larger in size than 850 microns without significantly decreasing throughput.

Variation of the wet granulation and wet milling parameters discussed above
5 can be employed to adjust the granule size distributions. For example, a slight decrease in particle size has been observed as mixing time increases for mixtures containing lower water amounts. It is hypothesized that where the water concentration is too low to fully activate the binder employed, the cohesive forces between the particles are insufficient to survive the shearing forces generated by the
10 mixing blades and granule size attrition rather than growth occurs. To the contrary, increasing the amount of water to fully activate the binder allows the cohesive forces between the particles to survive the shearing forces generated by the mixing blades and granule growth rather than attrition occurs with increased mixing time and/or water addition rate. Variation of the screen size of the wet mill tended to have a
15 greater impact on the granule size than variation of the feed rate and/or mill speed.

The dry granules are then placed in a suitable blender, such as a twin-shell blender, and the lubricant (such as magnesium stearate) and any additional carrier materials are added (such as the extragranular microcrystalline cellulose and extragranular croscarmellose sodium in certain tablet formulations). Blending times
20 depend in part upon the process equipment employed. For the 100 mg dose capsules and 200 mg dose capsules (1080 kg and 918 kg batches) discussed above, blending times of at least about 5 minutes at blender loads ranging from about 15% to about 60% and blender rotational speeds of at least about 10 revolutions per minutes consistently provided a blended material that was extremely
25 uniform with respect to celecoxib concentration. The relative standard deviations measured for unit dose blend samples were 3.9% or less and 2.2% or less for the 100 mg and 200 mg dose capsules, respectively. Where the diluents include microcrystalline cellulose, the addition of a portion of the microcrystalline cellulose during this step has been found to materially increase granule compressibility and
30 tablet hardness. In addition, increasing the amount of magnesium stearate above about 1% to about 2% was observed to decrease tablet hardness and increase friability and dissolution time.

This blended mixture is then encapsulated (or, if tablets are to be prepared, compressed into tablets to the desired weight and hardness using appropriate size

tooling). Conventional compression and encapsulation techniques known to those of ordinary skill in the art can be employed. Suitable results were obtained for capsules by employing bed heights ranging from about 20 mm to about 60 mm, compaction settings ranging from about 0 to about 5 mm, and speeds from about 60,000 capsules per hour to about 130,000 capsules per hour. Weight control of the dose was observed to decrease with either (i) low speed and high compaction, or (ii) high speed and low bed heights. Accordingly, these combinations of parameters preferably are carefully controlled. It was also discovered that slug formation can be minimized or eliminated by using the lowest compaction setting at which capsule weight control can be maintained. Where coated tablets are desired, conventional coating techniques known to those of ordinary skill in the art can be employed.

This combination of unit operations produces granules that are uniform in celecoxib content at the unit dose level, that readily dissolve in vitro, that flow with sufficient ease so that weight variation can be reliably controlled during capsule filling or tableting, and that are dense enough in bulk so that the batch can be processed in the selected equipment and individual doses fit into the specified capsules or tablet molds.

Use in the Preparation of Medicaments

The present invention also is directed to the use of the compositions of the present invention in the preparation of medicaments useful in the treatment and/or prophylaxis of cyclooxygenase-2 mediated conditions and disorders.

The following examples illustrate aspects of the present invention but should not be construed as limitations. The experimental procedures used to generate the data shown are discussed in more detail below. The symbols and conventions used in these examples are consistent with those used in the contemporary pharmacological literature. Unless otherwise stated, (i) all percentages recited in these examples are weight percents based on total composition weight, (ii) total composition weight for capsules is the total capsule fill weight and does not include the weight of the actual capsule employed, and (iii) coated tablets are coated with a conventional coating material such as Opadry White YS-1-18027A and the weight fraction of the coating is about 3% of the total weight of the coated tablet.

Example 1: 100 mg Dose Capsule

A capsule was prepared having the following composition:

Table 1

| INGREDIENT | WEIGHT FRACTION (%) | AMOUNT (mg) |
|---------------------------------------|--------------------------|----------------|
| Celecoxib | 37.04 | 100 |
| Lactose Monohydrate (NF, Ph Eur) | 55.46 | 149.75 |
| Sodium Lauryl Sulfate (NF, Ph Eur) | 3 | 8.1 |
| Povidone (K29-32 USP) | 2.5 | 6.75 |
| Croscarmellose Sodium (NF, Ph Eur) | 1 | 2.7 |
| Magnesium Stearate (NF, Ph Eur) | 1 | 2.7 |
| Total Capsule Fill Weight | 100 | 270 |

The above unit dose composition was placed in a hard gelatin capsule (white opaque, size #2) comprising titanium dioxide (USP), gelatin (NF), and blue ink (SB-6018).

The lactose monohydrate used in each of the examples of the application is commercially available from Formost Farms, Baraboo, Wisconsin. The Ac-Di-Sol brand of croscarmellose sodium used in each of the examples of the application is commercially available from FMC Corporation, Chicago, Illinois. The sodium lauryl sulfate used in each of the examples of the application is commercially available from Henkel Corporation, Cincinnati, Ohio. The Povidone brand of polyvinylpyrrolidone was used in each of the examples of the application and is commercially available from International Specialty Products. The magnesium stearate used in each of the examples of the application is commercially available from Mallinckrodt Inc., St. Louis, Missouri. The Opadry White YS-1-18027A used to

prepare the coated tablets disclosed in the examples of this application is a ready to coat coating formulation commercially available from Colorcon, West Point, Pennsylvania.

5 Capsule dose strengths between 25 mg to 225 mg can be accommodated by increasing or decreasing the amount of lactose as necessary to provide a total fill weight of 270 mg.

Example 2: 200 Mg Dose Capsule

10 A capsule was prepared having the following composition:

Table 2

| INGREDIENT | WEIGHT FRACTION (%) | AMOUNT (mg) |
|-------------------------------------|---------------------|-------------|
| Celecoxib | 74.07 | 200 |
| 15 Lactose Monohydrate (NF, Ph Eur) | 18.43 | 49.75 |
| Sodium Lauryl Sulfate (NF, Ph Eur) | 3 | 8.10 |
| 20 Povidone (K29-32 USP) | 2.5 | 6.75 |
| Croscarmellose Sodium | 1 | 2.7 |
| Magnesium Stearate (NF, Ph Eur) | 1 | 2.7 |
| 25 Total Capsule Fill Weight | 100 | 270 |

The above unit dose composition was placed in a hard gelatin capsule (white opaque, size #2) comprising titanium dioxide (USP), gelatin (NF), and blue ink (SB-6018).

30 **Example 3: 100 mg Dose Tablet**

Tablets were prepared having the following composition:

Table 3

| INGREDIENT | AMOUNT (mg/tablet) | WEIGHT FRACTION (%) | AMOUNT/ SECTION (kg/batch) |
|--|-----------------------|---------------------------|----------------------------------|
| Celecoxib | 100 | 40 | 6.40 |
| Lactose Monohydrate (NF) | 101.88 | 40.75 | 6.52 |
| Sodium Lauryl Sulfate (NF) | 7.5 | 3 | 0.48 |
| Povidone (K29/32, USP) | 6.25 | 2.5 | 0.40 |
| Croscarmellose Sodium (Type A, NF) | 7.5 | 3 | 0.48 |
| Microcrystalline Cellulose (Avicel PH-102, NF) | 25 | 10 | 1.60 |
| Magnesium Stearate (NF) | 1.88 | 0.75 | 0.12 |
| Total | 250.01 | 100 | 16 |
| Opadry White YS-1- 18027A | 7.50 | | |

The tablets prepared were 0.2100 inch X 0.4650 inch modified oval shaped tablets.

The Avicel brand of microcrystalline cellulose was used in the preparation of the tablets of Examples 3 and 4 and is commercially available from FMC Corporation, Philadelphia, Pennsylvania.

Tablet dose strengths between 25 mg to 225 mg can be accommodated by increasing or decreasing the amounts of celecoxib and each of the carrier materials described above so as to maintain the same weight fractions exemplified above.

Example 4: 200 Mg Dose Tablet

Tablets were prepared having the following composition:

Table 4

| INGREDIENT | AMOUNT (mg/tablet) | WEIGHT FRACTION (%) | AMOUNT/ SECTION (kg/batch) |
|---|-----------------------|---------------------------|----------------------------------|
| Celecoxib | 200 | 40 | 6.40 |
| Lactose Monohydrate (NF) | 203.75 | 40.75 | 6.52 |
| Sodium Lauryl Sulfate (NF) | 15 | 3 | 0.48 |
| Povidone (K29/32, USP) | 12.5 | 2.5 | 0.40 |
| Croscarmellose Sodium (Avicel PH-102, NF) | 15 | 3 | 0.48 |
| Microcrystalline Cellulose (Type A, NF) | 50 | 10 | 1.60 |
| Magnesium Stearate (NF) | 3.75 | 0.75 | 0.12 |
| Total | 500 | 100 | 16 |
| | | | |
| Opadry White YS-1- 18027A | 15.0 | | |

The tablets prepared were 0.2750 inch X 0.4960 inch modified capsule shaped tablets.

Example 5: Disintegration Tests

Six identical tablets were separately placed into one of six tubes having a wire mesh screen bottom in a disintegration basket. A water bath was preheated to $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and maintained at that temperature for the duration of the disintegration test. A 1000 mL beaker was placed in the water bath. The beaker was filled with a sufficient amount of water to ensure that the wire mesh screen of the tubes would remain at least 2.5 cm below the water surface during the test. The disintegration basket was inserted in the water at time = 0 minutes and repeatedly raised and lowered until the test was complete while maintaining the wire mesh screen of the tubes at least 2.5 cm below the water surface. Disintegration time for each tablet was the time at which the very last portion of the tablet passed through the screen at the bottom of the tube. The mean results for the uncoated tablets of Examples 3 and 4 are reported in Table 5.

Table 5

| TABLET | DISINTEGRATION TIME (MINUTES) |
|--|----------------------------------|
| Example 3: 100 mg Dose Tablet (Uncoated) | 4 minutes, 35 seconds |
| Example 4: 200 mg Dose Tablet (Uncoated) | 7 minutes, 40 seconds |

Example 6: Dissolution Tests

The apparatus of U.S.P. II (with paddles) was used to determine the dissolution rate of the capsules of Examples 1 and 2 and the uncoated tablets of Examples 3 and 4. A 1000 mL 1% sodium lauryl sulfate/0.04M Na_3PO_4 (pH = 12) solution was used as the dissolution fluid. The solution was maintained at a temperature of $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ and stirred at 50 rpm during the test. Twelve identical tablets or capsules were tested. The 12 tablets or capsules were each separately placed in one of 12 standard dissolution vessels and time = 0 minutes. At time = 15, 30, 45 and 60 minutes, a 5 mL aliquot of solution was removed from each vessel. The sample from each vessel was filtered and the absorbance of the sample measured (UV spectrophotometer; 2 mm pathlength quartz cell; 243 nm or wavelength of UV maxima; blank: dissolution medium). Percent dissolution was

calculated based on the measured absorbances. The mean results of the dissolution tests are reported in Table 6.

Table 6

| DOSAGE FORM | % DISSOLVED | | | |
|--------------------------------|-------------|------------|------------|------------|
| | 15 minutes | 30 minutes | 45 minutes | 60 minutes |
| Example 1: 100 mg Dose Capsule | 89 | 99 | 100 | 100 |
| Example 2: 200 mg Dose Capsule | 55 | 82 | 89 | 92 |
| Example 3: 100 mg Dose Tablet | 81 | 93 | 94 | 95 |
| Example 4: 200 mg Dose Tablet | 60 | 96 | 98 | 98 |

Example 7: Particle Size Analysis

Table 7A shows the results of a particle size sieve analysis of the wet granulated pharmaceutical compositions of Examples 1 and 2, respectively, prior to encapsulation. The column entitled "Percent Retained On Screen" reports the percent of the total batch having a particle size larger than the indicated sieve size.

Table 7A

| SIEVE SIZE (MICRONS) | EXAMPLE 1 (100 mg DOSE CAPSULE): PERCENT RETAINED ON SCREEN | | EXAMPLE 2 (200 mg DOSE CAPSULE): PERCENT RETAINED ON SCREEN | |
|----------------------|---|-------------|---|-------------|
| | Lower Limit | Upper Limit | Lower Limit | Upper Limit |
| 850 | 0 | 1.3 | 1.1 | 10.7 |
| 425 | 2.8 | 14.9 | 4.3 | 25.4 |
| 250 | 10.0 | 25.5 | 10.8 | 35.4 |
| 180 | 15.3 | 39.0 | 17.3 | 39.2 |
| 106 | 32.5 | 64.5 | 35.2 | 58.2 |
| 75 | 37.1 | 77.5 | 39.5 | 71.8 |
| 0 | 100 | 100 | 100 | 100 |

Table 7B shows the results of a particle size sieve analysis of the wet granulated pharmaceutical compositions of Examples 3 and 4, respectively, prior to compression into the tablets. The column entitled "Percent of Batch" reports the percent of the total batch having a particle size between the indicated sieve size and the next smaller sieve size indicated. The column entitled "Cumulative Percent of Batch" reports the percent of the total batch having a particle size larger than the indicated sieve size.

Table 7B

| SIEVE SIZE (MICRONS) | EXAMPLE 3 (100 mg DOSE TABLET) | | EXAMPLE 4 (200 mg DOSE TABLET) | |
|-----------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| | Percent of Batch | Cumulative Percent of Batch | Percent of Batch | Cumulative Percent of Batch |
| 840 (20 mesh screen) | 1 | 1 | 0.79 | 0.79 |
| 420 (40 mesh screen) | 24.6 | 25.6 | 24.85 | 25.64 |
| 250 (60 mesh screen) | 18.4 | 44 | 19.13 | 44.77 |
| 177 (80 mesh screen) | 9.6 | 53.6 | 11.05 | 55.82 |
| 149 (100 mesh screen) | 6.6 | 60.2 | 6.9 | 62.72 |
| 105 (140 mesh screen) | 11.6 | 71.8 | 11.44 | 74.16 |
| 74 (200 mesh screen) | 8.8 | 80.6 | 8.28 | 82.45 |
| Fines | 19.4 | 100 | 17.55 | 100 |

Example 8: Bulk Density Analysis

Table 8 shows the results of a bulk density analysis of the wet granulated pharmaceutical compositions of Examples 1, 2, 3 and 4 prior to encapsulation or compression into tablets:

Table 8

| COMPOSITION | BULK DENSITY (g/mL ³) | TAPPED DENSITY (g/mL ³) | LOSS ON DRYING (%) |
|-----------------------------------|--------------------------------------|--|--------------------------|
| Example 1: 100 mg Dose Capsule | 0.77 | 1.02 | 0.6 |
| Example 2: 200 mg Dose Capsule | 0.61 | 0.96 | 0.5 |
| Example 3: 100 mg Dose Tablet | 0.73 | 0.87 | 1.37 |
| Example 4: 200 mg Dose Tablet | 0.72 | 0.86 | 1.4 |

Example 9: Tablet Analysis Program

Table 9 shows the results of the tablet analysis program ("TAP analysis") for a sampling of tablets of having the composition of the tablets of Examples 3 and 4.

Table 9

| TABLETS TESTED (N = 10) | AVERAGE WEIGHT (mg) | AVERAGE THICKNESS (inches) | HARDNESS (kP) |
|----------------------------------|------------------------|----------------------------------|---------------|
| Example 3: 100 mg Dose Tablet | 248 | 0.1605 | 8.2 |
| Example 4: 200 mg Dose Tablet | 500 | 0.2177 | 14.6 |

Example 10: Friability Test

Tablets collectively weighing 12 g were placed in a rotating drum. Extraneous dust was first removed from the drum and the tablets. The drum was started and rotation continued for ten minutes at a minimum of 25 rotations per minute. The rotation of the drum was stopped and the tablets removed. Loose dust on the tablets as well as any broken tablets were removed and the intact tablets were weighed. The percent loss of the test samples from Examples 3 and 4 was calculated and is reported below in Table 10.

Table 10

| TABLETS | PERCENT LOSS |
|-------------------------------|--------------|
| Example 3: 100 mg Dose Tablet | 0.33 |
| Example 4: 200 mg Dose Tablet | 0.16 |

Example 11: Effect Of Formulating Variables On Relative Bioavailability, Wetting Performance, And Disintegration Performance

The effect of such formulation parameters as drug particle size, increased concentrations of surfactant, pH, and dispersibility were evaluated relative to oral solutions and unformulated drug in a capsule in a dog model. The effect of micronizing celecoxib (mean particle size 10-20 microns) was tested in formulation A. The combined effect of micronization, added surfactant (sodium lauryl sulfate), and increased micro-environmental pH ($\text{Na}_3\text{PO}_4\text{H}_2\text{O}$) was tested in formulation B. The effect of bringing the surfactant (Tween 80) into intimate contact with celecoxib (co-precipitating vs. simple dry mixing) was tested in formulation C. The effect of further reducing particle size (approximating one micron) and dispersing the particles in a suspension was tested in formulation D. A solution of celecoxib (formulation E) and unmilled, unformulated celecoxib in a capsule (formulation F) were included as references. The specific compositions of formulations A, B, C, D, E and F are summarized in Table 11A.

Table 11A

| INGREDIENT | WEIGHT FRACTION (%) | | | | | |
|--|---------------------|-----|-----|-----|-----|-----|
| | A | B | C | D | E | F |
| celecoxib (micronized) | 25 | 25 | | | | |
| celecoxib/tween 80 ⁽¹⁾ | | | 25 | | | |
| celecoxib (dispersed) ⁽²⁾ | | | | 100 | | |
| celecoxib (solution) | | | | | 100 | |
| celecoxib (unmilled) | | | | | | 100 |
| sodium lauryl sulfate | 2 | 25 | | | | |
| Avicel 101 | 73 | 25 | 75 | | | |
| Na ₃ PO ₄ H ₂ O | | 25 | | | | |
| Total | 100 | 100 | 100 | 100 | 100 | 100 |

⁽¹⁾ Precipitated from ethanol solution using 5% Tween 80 in water solution as an antisolvent.

⁽²⁾ Prepared as a suspension by ball-milling the drug in a slurry of polysorbate 80 and polyvinylpyrrolidone until particles were approximately one micron in diameter as estimated by microscopy.

⁽³⁾ Solution in polyethylene glycol 400:water (2:1 v/v).

The formulations were administered to groups of three male and female dogs. Group 1 dogs were administered celecoxib as the solution and in capsule formulations A and B in a nonrandomized crossover design. Group 2 dogs were administered celecoxib in capsule formulation C and suspension D in a capsule in a nonrandomized crossover design. Plasma samples were collected over a 24-hour period and analyzed for celecoxib with an HPLC method.

The results of the study (Tables 11B and 11C) indicated that decreasing the particle size (A), increasing the pH (B) or increasing the wetting (C) increased the availability (as measured by AUC_(0-24 hrs)) of celecoxib compared to earlier studies of unformulated drug in a capsule. The availability of celecoxib was greater from the PEG:H₂O solution and the suspension (D). The availability from the suspension was approximately the same as from the solution and indicated that celecoxib availability can be improved by celecoxib particle size control (such as pin milling of celecoxib),

increased wetting of the celecoxib (such as by including sodium lauryl sulfate in the granulating fluid) and improved dispersibility (such as by including croscarmellose sodium in the granulation).

Table 11B

| Time (hours) | Blood Serum Celecoxib Concentration (µg/mL) | | | | | |
|--------------|---|----------------|----------------|--------|----------------|----------------------------------|
| | A | B ¹ | C ¹ | D | E ¹ | F ¹ |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0.5 | 0.0143 | 0.247 | 0.0635 | 0.453 | 0.824 | 0.205 |
| 1.0 | 0.244 | 0.228 | 0.443 | 0.826 | 0.820 | 0.333 |
| 2.0 | 0.318 | 0.138 | 0.717 | 0.865 | 0.604 | 0.262 |
| 3.0 | 0.189 | 0.0860 | 0.492 | 0.741 | 0.517 | 0.517 |
| 4.0 | 0.145 | 0.0707 | 0.384 | 0.576 | 0.413 | 0.234 |
| 6.0 | 0.107 | 0.0664 | 0.233 | 0.354 | 0.286 | 0.197 (measured at 7.0 hours) |
| 8.0 | 0.0828 | 0.0624 | 0.160 | 0.234 | 0.187 | -- |
| 12.0 | 0.0939 | 0.0431 | 0.0865 | 0.142 | 0.0802 | -- |
| 24.0 | -- | 0.0404 | 0.0408 | 0.0394 | 0.0159 | -- |

¹ Micronized celecoxib.

Table 11C

| Pharmacokinetic Parameter | Pharmacokinetic Parameter Value ¹ | | | | | |
|------------------------------|--|----------------|----------------|-------------|----------------|----------------|
| | A | B ² | C ² | D | E ² | F ² |
| C _{max} (µg/mL) | 0.36 ± 0.06 | 0.45 ± 0.18 | 0.79 ± 0.19 | 1.01 ± 0.27 | 1.52 ± 0.20 | 0.5 |
| T _{max} (hours) | 1.3 ± 0.2 | 0.7 ± 0.2 | 1.5 ± 0.3 | 1.7 ± 0.27 | 1.52 ± 0.20 | 3.0 |
| Relative Bioavailability (%) | 31.2 ± 2.9 | 24.9 ± 1.4 | 46.3 ± 9.5 | 69.5 ± 9.6 | 89.4 ± 4.5 | 16.9 |

¹ N = 3 except for Formulation F where N = 3.

² Micronized celecoxib.

Various formulations containing sodium lauryl sulfate (0-5% w/w) and sodium croscarmellose (0-5%) were screened for relative wettability and disintegration tendency. Relative wettability was estimated by measuring the time required for water to penetrate a column of granulated material prepared from each formulation. Disintegration tendency was determined by measuring the weight of granulated material retained on a #20 (850 μ m) screen after soaking the material in 37°C water for 5 minutes. The specific compositions of formulations A through H evaluated are summarized in Table 11D.

Table 11D

| Formulation | WEIGHT FRACTION (%) | | | | | | | |
|-----------------------|---------------------|------|------|------|------|------|------|------|
| | A ⁽¹⁾ | B | C | D | E | F | G | H |
| Celecoxib | 74.7 | 74.7 | 74.7 | 74.7 | 74.7 | 74.7 | 74.7 | 74.7 |
| Lactose | 15.8 | 15.8 | 21.8 | 19.8 | 17.8 | 15.8 | 17.8 | 11.8 |
| Polyvinyl-pyrrolidone | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Sodium Lauryl Sulfate | 3.0 | 3.0 | 0.0 | 1.0 | 1.0 | 1.0 | 3.0 | 5.0 |
| Ac-di-sol | 3.0 | 3.0 | 0.0 | 1.0 | 3.0 | 5.0 | 1.0 | 5.0 |
| Magnesium Stearate | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |

⁽¹⁾Sodium lauryl sulfate was added as a dry powder

Results are summarized in Table 11E. Penetration tests were done in triplicate. Disintegration tests were done in duplicate. Results of the penetration study indicated that wet application of sodium lauryl sulfate (Formulation B) was superior to dry application (formulation A) and that formulations containing 3 to 5 weight percent sodium lauryl sulfate (formulations B, G, and H) were superior to those with lesser amounts of sodium lauryl sulfate (formulations C through F). Formulations containing 3% sodium lauryl sulfate (formulations B and G) were similar to those containing 5% (formulations H). Results of the disintegration study indicated that complete disintegration could be achieved with sodium croscarmellose concentrations as low as 1% (formulation G) at surfactant concentrations of 3%. Complete disintegration could also be achieved with higher

amounts of disintegrant (formulations B, F, and H) regardless of surfactant concentration. Formulation G exhibited both superior penetration and complete disintegration with the minimum amount of excipient required.

Table 11E

| Formulation | % Sodium Lauryl Sulfate/% Ac-di-sol | Penetration Time (n=3) | Disintegration (n=2) |
|------------------|-------------------------------------|------------------------|----------------------|
| A ⁽¹⁾ | 3/3 | >18 hours | 0.1-0.5% |
| B | 3/3 | 5-60 minutes | none detected |
| C | 0/0 | >4 to >18 hours | 20-26% |
| D | 1/1 | >4 to >18 hours | 10-13% |
| E | 1/3 | 2 to 4 hours | 4-6% |
| F | 1/5 | 1 to 4 hours | none detected |
| G | 3/1 | 10 to 40 minutes | none detected |
| H | 5/5 | 10 to 55 minutes | none detected |

⁽¹⁾ Sodium lauryl sulfate was added as a dry powder

Example 12

The following formulations were evaluated for wetting effects and mixture uniformity:

Table 12

| INGREDIENT | WEIGHT FRACTION (%) | | | | | | | |
|----------------------------|---------------------|------|--------------------------------------|------|--|-----|---|------|
| | Lactose Dry Blend | | Microcrystalline Cellulose Dry Blend | | Polyvinyl-pyrrolidone Granulation ¹ | | Polysorbate 80 Granulation ² | |
| Celecoxib | 5 | 60 | 5 | 60 | 5 | 60 | 5 | 60 |
| Lactose | 94.5 | 39.5 | -- | -- | 92 | 37 | 93.5 | 38.5 |
| Microcrystalline Cellulose | -- | -- | 94.5 | 39.5 | -- | -- | -- | -- |
| Polysorbate 80 | -- | -- | -- | -- | -- | -- | 1.0 | 1.0 |
| Povidone (K29-32) | -- | -- | -- | -- | 2.5 | 2.5 | -- | -- |
| Magnesium Stearate | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |

¹ In this formulation polyvinylpyrrolidone was added to the blend as a dry powder prior to granulation with water.

² In this formulation celecoxib and lactose were granulated with an aqueous solution of polysorbate 80.

The 5% celecoxib blends exhibited better blend homogeneity than the 60% celecoxib blends. The measured relative standard deviations for the 5% celecoxib blends ranged from 0.4% to 3.5% while the measured relative standard deviations for the 60% celecoxib blends ranged from 4.7% to 6.3%. In addition to being less homogeneous, the 60% celecoxib blends contained relatively large granules (greater than 420 microns) that were superpotent (containing 124% to 132% higher concentrations of celecoxib relative to other granules).

Four similar formulations were prepared containing 25% celecoxib loading instead of 5% or 60% celecoxib loading as above. The bioavailability of these formulations was evaluated in a dog model. The polyvinylpyrrolidone wet

granulation formulation exhibited the highest bioavailability with a formulation efficiency of about 74%.

Example 13

Capsules having the following formulations were prepared and evaluated:

Table 13A

| INGREDIENT | AMOUNT (mg) | | |
|--------------------|-------------------|--------------------|---------------------|
| | 5 mg Dose Capsule | 20 mg Dose Capsule | 100 mg Dose Capsule |
| Celecoxib | 5 | 20 | 100 |
| Lactose | 92 | 77 | 61.9 |
| Povidone (K29-32) | 2.5 | 2.5 | 4 |
| Magnesium Stearate | 0.5 | 0.5 | 0.8 |
| Total | 100 | 100 | 166.7 |
| | | | |
| Capsule Shell | 1 | 1 | 1 |
| Capsule Size | #3 | #3 | #3 |

The celecoxib was milled by multiple passes through an oscillating mill fitted with successively smaller screen sizes (#14, #20, #40). The particle size of at least 90% of the celecoxib particles added to this mixture was less than about 37 microns. Celecoxib, lactose and polyvinylpyrrolidone were mixed in a planetary mixer bowl and wet-granulated with water. The granulation was then tray dried at 60°C, milled through a 40 mesh screen, lubricated with magnesium stearate in a V-blender and encapsulated on a dosator-type encapsulator. The in vitro dissolution profile of the capsules was determined using USP method 2 and a dissolution media of a 15 mM phosphate buffer at pH 10. About 50% in vitro dissolution was achieved after about 15 minutes with greater than 95% in vitro dissolution after about 30 minutes.

The absorption, distribution, metabolism and elimination profile of this 100 mg dose capsule was compared to the profile of a suspension of [C¹⁴]celecoxib. The

study was an open-label, randomized crossover study carried out in ten healthy male subjects. The suspension was prepared by dissolving celecoxib in ethanol containing 5% polysorbate 80 and adding that mixture to apple juice prior to administration. Subjects receiving the suspension ingested a 300 mg dose of celecoxib. Subjects receiving capsule-form celecoxib received three 100 mg dose capsules for a total dose of 300 mg of celecoxib. The rate of absorption from the capsule was slower than from the suspension, but was equivalent to the suspension when measured by $AUC_{0-48 \text{ hrs}}$. Mean results are reported in Table 13B below. $[C^{14}]$ Celecoxib was largely metabolized with only about 2.56% of the radioactive dose in either urine or feces.

Table 13B

| PHARMACOKINETIC PARAMETER | CELECOXIB SUSPENSION | CELECOXIB CAPSULES |
|------------------------------|-------------------------|-----------------------|
| $AUC_{(0-48)} ((ng/ml)hr)$ | 8706.7 | 8763.1 |
| $C_{max} (ng/ml)$ | 1526.5 | 1076.5 |
| $T_{max} (hr)$ | 1.42 | 1.94 |
| $T_{1/2} (hr)$ | 11.53 | 15.57 |

Example 14

Capsules having the following formulations were prepared and evaluated:

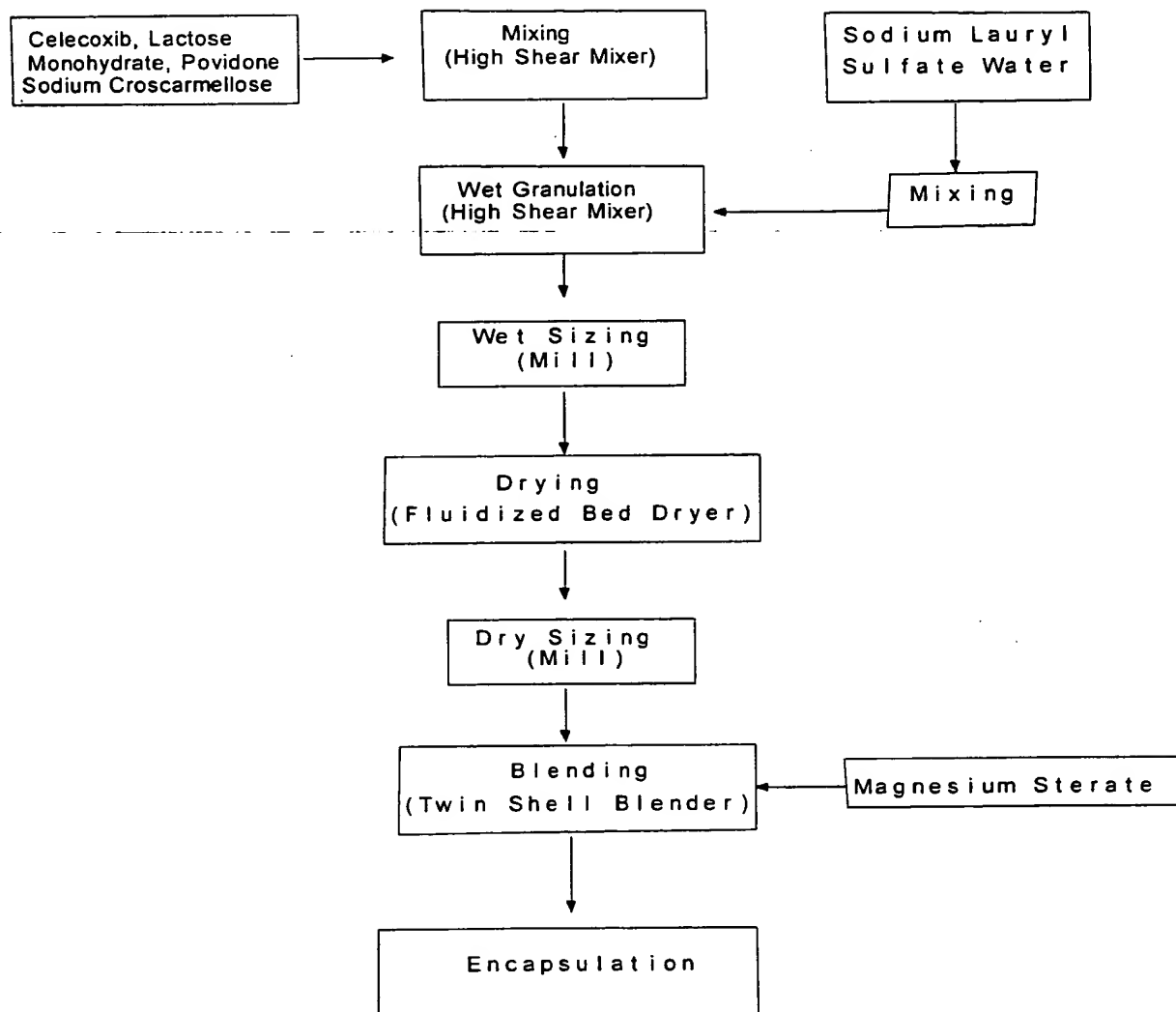
Table 14

| INGREDIENT | AMOUNT (mg) | |
|--------------------|----------------|----------------|
| | 100 mg Capsule | 200 mg Capsule |
| Celecoxib | 100 | 200 |
| Lactose | 223.4 | 120.1 |
| Povidone (K29-32) | 8.3 | 8.3 |
| Magnesium Stearate | 1.7 | 5 |
| Total | 333.4 | 333.4 |
| Capsule Size | #1 | #1 |

These formulations were prepared in a manner similar to the formulations of Example 13 except that an impact-type pin mill was used instead of an oscillating mill. Particle size was further reduced by use of the pin mill. For the 100 mg dose capsule about 30% in vitro dissolution was achieved after about 15 minutes with greater than 85% in vitro dissolution after about 30 minutes. For the 200 mg capsule about 50% in vitro dissolution was achieved after about 15 minutes with greater than 85% in vitro dissolution after about 30 minutes.

Example 15: Preparation of 100 mg Dose Capsules

The 100 mg dose and 200 mg dose capsules of Examples 1 and 2, respectively, can be prepared in accordance with acceptable pharmaceutical manufacturing practices in the manner illustrated by the flow diagram below. The 100 mg dose and 200 mg dose tablets of Examples 3 and 4, respectively, can be prepared by appropriately modifying this process to account for the extragranular addition of croscarmellose sodium and microcrystalline cellulose, and tableting instead of encapsulating the composition.



An illustrative process for the bulk formulation of 100 mg dose capsules using the starting materials described below. A typical batch consists of four identical granulation sections, although the number of granulation sections is not narrowly critical and depends largely upon equipment handling capacity and batch size needed.

Milling: The celecoxib was milled in an impact-type pin mill with counter rotating disks. At mill speeds ranging from about 8960 rpm/5600 rpm to about 11200 rpm/5600 rpm (rotating rpm/counter rotating rpm) particle size varied within relatively narrow ranges (at least 90% of the particles were 30 microns or less in size) suggesting that mill speed is not narrowly critical to the bulk drug micronization process.

Dry Mixing: The celecoxib, lactose, Povidone and croscarmellose sodium were transferred to a 120 L Niro Fielder PMA-120 high speed granulator and mixed for about 3 minutes at fast chopper and impeller speeds. This dry mixing time provided adequate mixing of celecoxib with the carrier materials prior to the start of the wet granulation step.

Wet Granulation: Sodium lauryl sulfate (8.1 kg) was dissolved in purified USP water (23.7 kg). This solution was progressively added to the granulator at a rate of about 14 kg/minute. Total granulation time was about 6.5 minutes. During this granulation, the main blade and chopper blade of the granulator were placed on the fast speed setting. The wet granulated mixture was about 8.1% water by weight.

Drying: The wet granulation was delumped using a Quadro Comil Model 198 S screening mill equipped with rotating impeller and a coarse screen. Wet milling was used to eliminate large material lumps that formed as a by-product of the wet granulation operation. If not removed, these lumps would have prolonged the subsequent fluidized bed drying operation and increase the variation with respect to moisture control. The delumped granulation was transferred to an Aeromatic Fluid Bed Dryer T-8. The inlet air temperature and flow rate were adjusted to about 60°C and about 5000 to 6000 ft³/minute. The granulation was dried in the fluidized bed dryer to reduce the moisture content to between 0.5% to 2.5%. Moisture content

was monitored using a Computrac Moisture Analyzer. Drying continued until the loss on drying of the granulation was not more than 1.0%. It may be desirable to combine two or more granulation sections for this drying step and subsequent processing steps.

5 Dry Milling: The dry granules were passed through a Fluid Air Mill Model 007 impact mill (conventional hammer) equipped with a 0.028 inch to 0.063 inch screen, knives forward, and 2400 rpm speed. Dry milling was used in combination with the wet granulation step to control the final size distribution of the granules.

10 Blending and Lubrication: The milled granules were then placed in a PK Cross-Flow Blender 75 Cubic Foot diffusion mixer/V- blender. The magnesium stearate was added and the mixture blended for about 5 minutes. The blending time provided blended material that was uniform with respect to the concentration of celecoxib.

15 Blender rotational speed was 10.6 revolutions per minute. The final blend was used to combine materials from multiple granulation sections into a single uniform mixture and to evenly distribute lubricant into the material prior to encapsulation into final dosage units.

20 Encapsulation: The granulated powder blend was encapsulated using an MG2 G100 encapsulator and an MG2 G120 piston. The capsules were polished.

The above sequence of unit operations produced granules that were highly uniform in celecoxib content at the unit dose level, that readily dissolved in vitro, that flowed with sufficient ease so weight variation could be reliably controlled during capsule filling, and that were dense enough in bulk so that the batch could be processed in the selected equipment and individual doses fit into the specified capsules.

25

Example 16: Bioequivalency Study

30 The bioequivalency and safety of 200 mg doses of celecoxib were evaluated in an open-label, randomized, single dose, three-way crossover study of a group of 46 healthy adult humans. The subjects received three single 200 mg doses celecoxib administered as (A) one 200 mg dose capsule, (B) two 100 mg dose capsules, (C) two 100 mg dose capsules (from a different batch run). Treatments

were separated by seven days. The specific pharmaceutical compositions of the 100 mg dose capsule and the 200 mg dose capsules are disclosed in Examples 1 and 2, respectively. The subjects, who had fasted overnight, received single oral doses of the study medication together with about 180 mL of water at 0800 hours.

5 The subjects continued to fast and remained in an upright position for four hours after dose administration. Blood samples were collected at -0.25 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours post dose. Analyses of the separated plasma were performed at PPD Pharmaco, Richmond, VA. Celecoxib plasma concentrations were determined using a validated high performance liquid

10 chromatography ("HPLC") procedure with a lower limit of detection of 10.0 ng/mL. Each subject was separately tested after receiving one 200 dose mg capsule and after receiving two 100 mg dose capsules. A minimum of a seven day wash-out period was allowed between administration of each single 200 mg dose. The mean results obtained from the 46 subjects tested are reported in Tables 16A and 16 B

15 below.

Table 16A

| TIME (hours) | PLASMA CONCENTRATION OF CELECOXIB (ng/mL) | | |
|-----------------|---|--|---|
| | One 200 mg Dose Capsule (Example 2) | Two 100 mg Dose Capsules (Example 1-- Batch 1) | Two 100 mg Dose Capsules (Example 1--Batch 2) |
| -0.25 | 0.22 | 0.00 | 0.00 |
| 0.5 | 103.74 | 117.89 | 212.61 |
| 1.0 | 418.24 | 446.39 | 647.00 |
| 1.5 | 575.68 | 606.97 | 826.90 |
| 2.0 | 646.83 | 656.98 | 862.23 |
| 3.0 | 686.19 | 666.55 | 781.13 |
| 4.0 | 621.02 | 595.21 | 660.15 |
| 6.0 | 389.00 | 387.41 | 383.81 |
| 8.0 | 322.24 | 332.51 | 323.59 |
| 12.0 | 214.63 | 208.06 | 209.96 |
| 16.0 | 149.11 | 146.40 | 144.23 |
| 24.0 | 116.09 | 111.77 | 113.21 |
| 36.0 | 52.76 | 48.27 | 46.98 |
| 48.0 | 27.24 | 26.47 | 22.44 |

Table 16B

| PHARMACO- KINETIC PARAMETER | PHARMACOKINETIC PARAMETER VALUE | | |
|---|---|---|---|
| | One 200 mg Dose Capsule (Example 2) | Two 100 mg Dose Capsules (Example 1--Batch 1) | Two 100 mg Dose Capsules (Example 1--Batch 2) |
| AUC ₍₀₋₄₈₎ ((ng/mL)hr) | 8107.07 | 7976.56 | 8535.49 |
| AUC _(0-LQC) ((ng/mL)hr) | 8063.17 | 7953.71 | 8501.94 |
| AUC _(0-∞ hours) ((ng/mL)hr) | 8828.64 | 8640.46 | 9229.52 |
| C _{max} (µg/mL) | 801.19 | 815.21 | 959.50 |
| T _{max} (hours) | 2.46 | 2.84 | 2.23 |
| T _½ (hours) | 12.22 | 13.52 | 10.67 |
| C _{max} /AUC _(0-LQC) | 0.10 | 0.10 | 0.20 |

Example 17: Effect of Food Study

An open-label randomized, single dose, four-way crossover study was employed to evaluate the dose proportionality and the effect of food on the pharmacokinetic profile of celecoxib in healthy adult subjects. Safety was assessed based on adverse events, vital signs and clinical laboratory tests. Twenty four healthy adult subjects were randomized to receive the following single doses of celecoxib: (A) a 50 mg dose capsule under fasting conditions, (B) a 50 mg dose capsule immediately following a high fat breakfast, (C) a 100 mg dose capsule under fasting conditions, and (D) a 100 mg dose capsule immediately following a high fat breakfast. The subjects received the study medication on days 1, 8, 15, and 22 in one of four treatment sequences (ADBC; BACD; CBDA; AND DCAB). The specific

composition of the 100 mg dose capsule is disclosed in Example 1. The specific composition of the 50 mg dose capsule is disclosed in Table 17A below:

Table 17A

| INGREDIENT | Amount (mg) |
|---------------------------|-------------|
| Celecoxib | 50.00 |
| Lactose Monohydrate | 199.8 |
| Sodium Lauryl Sulfate | 8.1 |
| Povidone (K29-32) | 6.8 |
| Croscarmellose Sodium | 2.7 |
| Magnesium Stearate | 2.7 |
| Total Capsule Fill Weight | 270.0 |

The above unit dose composition was placed in a hard gelatin capsule (white opaque, size #2).

Blood samples were collected at -0.25 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours post dose. Analyses of the separated plasma were performed at PPD Pharmaco, Richmond, VA. Celecoxib plasma concentrations were determined using a validated high performance liquid chromatography ("HPLC") procedure with a lower limit of detection of 10.0 ng/mL. There were no clinically significant changes in vital signs or physical examinations. All adverse events were mild in severity. The mean results obtained from the 24 subjects tested are reported in Tables 17B and 17C below.

Table 17B

| TIME (Hours) | PLASMA CONCENTRATION OF CELECOXIB (ng/mL) | | | |
|-----------------|---|--|---|---|
| | Single 100 mg dose capsule (fasting) | Single 100 mg dose capsule (high fat breakfast) | Single 50 mg dose capsule (fasting) | Single 50 mg dose capsule (high fat breakfast) |
| -0.25 | 0.00 | 0.00 | 0.00 | 0.00 |
| 0.5 | 63.96 | 1.35 | 52.90 | 2.38 |
| 1.0 | 225.65 | 14.00 | 155.07 | 11.98 |
| 1.5 | 344.77 | 49.37 | 202.22 | 29.85 |
| 2.0 | 354.45 | 139.43 | 220.15 | 63.00 |
| 3.0 | 348.03 | 438.99 | 253.85 | 186.94 |
| 4.0 | 333.86 | 600.00 | 244.80 | 298.23 |
| 6.0 | 196.53 | 355.65 | 118.58 | 188.90 |
| 8.0 | 152.35 | 314.54 | 91.79 | 165.85 |
| 12.0 | 121.08 | 179.04 | 61.13 | 88.76 |
| 16.0 | 86.13 | 102.12 | 39.51 | 51.86 |
| 24.0 | 61.77 | 49.31 | 28.22 | 22.81 |
| 36.0 | 38.00 | 17.88 | 10.69 | 8.75 |
| 48.0 | 17.77 | 7.91 | 5.77 | 3.80 |

Table 17C

| PHARMACO- KINETIC PARAMETER | PHARMACOKINETIC PARAMETER VALUE | | | |
|---|---|--|--|---|
| | Single 100 dose mg capsule (fasting) | Single 100 mg dose capsule (high fat breakfast) | Single 50 mg dose capsule (fasting) | Single 50 mg dose capsule (high fat breakfast) |
| AUC ₍₀₋₄₈₎ ((ng/mL)hr) | 4463.28 | 5214.86 | 2426.23 | 2601.10 |
| AUC _(0-LQC) ((ng/mL)hr) | 4415.59 | 5105.50 | 2352.68 | 2501.56 |
| AUC _(0-∞ hours) ((ng/mL)hr) | 5126.74 | 5419.21 | 2693.80 | 2759.42 |
| C _{max} (µg/mL) | 455.00 | 746.96 | 321.46 | 354.17 |
| T _{max} (hours) | 2.60 | 5.00 | 2.92 | 4.46 |
| T _½ (hours) | 16.02 | 6.86 | 11.01 | 6.49 |
| C _{max} /AUC _(0-LQC) | 0.11 | 0.15 | 0.16 | 0.16 |

Definitions

The term "active ingredient" means celecoxib.

The term "carrier material" means material added to a pharmaceutical composition to impart certain desirable properties. For example, in the case of a tablet, carrier material may be added to moderate dissolution rate, mask a bad taste, or improve appearance of the tablet.

The term "AUC₍₀₋₄₈₎" means the area under the plasma concentration-time curve from t=0 to t=48 in units of ((ng/mL)) hr determined using the linear trapezoidal rule.

The term "AUC_(0-LQC)" means the area under the plasma concentration-time curve from t=0 to the last quantifiable concentration ("LQC") in units of ((ng/mL)) hr determined using the trapezoidal rule.

The term "AUC_(0-∞)" is calculated as AUC_(0-LQC) + LQC/(-β), where LQC was the last quantifiable plasma concentration and β is the slope from the calculation of T(½) and has units of ((ng/mL)) hr.

The term "C_{max}" means the maximum observed concentration.

The term " T_{\max} " means the time at which C_{\max} occurred.

The term " $T_{1/2}$ " means the terminal half-life, in units of hours, determined via simple linear regression of natural log (ln) concentration vs. time for data points in the 'terminal phase' of the concentration-time curve. $T_{1/2}$ was computed as $-\ln(2)/(-\beta)$.

5 The term " $C_{\max}/AUC_{(0-LQC)}$ " means the rate of absorption.

As various changes could be made in the above formulations and methods without departing from the scope of the invention, it is intended that all matter contained in the above description be interpreted as illustrative and not in a limiting
10 sense. All patent documents listed herein are incorporated by reference.

What is claimed is:

1. A pharmaceutical composition suitable for oral administration comprising celecoxib in an amount from about 10 mg to about 1000 mg and polyvinylpyrrolidone.

2. A pharmaceutical composition according to Claim 1 wherein said celecoxib is present in an amount from about 50 mg to about 800 mg.
3. A pharmaceutical composition according to Claim 1 wherein said celecoxib is present in an amount from about 75 mg to about 400 mg.
4. A pharmaceutical composition according to Claim 1 wherein said celecoxib is present in an amount from about 100 mg to about 200 mg.
5. A pharmaceutical composition according to Claim 1 further comprising one or more pharmaceutically acceptable diluents, wherein said diluent or diluents are present in the range of about 5% to about 99% of the total weight of the composition.
6. A pharmaceutical composition according to Claim 5 wherein said diluents are selected from the group consisting of lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose, dibasic calcium phosphate, sucrose-based diluents, confectioner's sugar, monobasic calcium sulfate monohydrate, calcium sulfate dihydrate, calcium lactate trihydrate, dextrates, Celutab, inositol, hydrolyzed cereal solids, amylose, Rexcel, powdered cellulose, calcium carbonate, glycine, and bentonite.
7. A pharmaceutical composition according to Claim 5 wherein said diluents are selected from the group consisting of lactose and microcrystalline cellulose.
8. A pharmaceutical composition according to Claim 1 further comprising one or more pharmaceutically acceptable disintegrants, wherein said disintegrants

are present in the range of about 0.2% to about 30% of the total weight of the composition.

9. A pharmaceutical composition according to Claim 8 wherein said disintegrants are selected from the group consisting of starches, sodium starch glycolate, clays, celluloses, alginates, pregelatinized corn starches, crospovidone, and gums.
10. A pharmaceutical composition according to Claim 8 wherein said disintegrant comprises croscarmellose sodium.
11. A pharmaceutical composition according to Claim 1 further comprising one or more pharmaceutically acceptable wetting agents, wherein said wetting agents or wetting agents are present in the range of about 0.25% to about 15% of the total weight of the composition.
12. A pharmaceutical composition according to Claim 11 wherein said wetting agent comprises an anionic surfactant.
13. A pharmaceutical composition according to Claim 11 wherein said wetting agent comprises sodium lauryl sulfate.
14. A pharmaceutical composition according to Claim 1 further comprising one or more pharmaceutically acceptable lubricants, wherein said lubricant or lubricants are present in the range of about 0.1% to about 10% of the total weight of the composition.
15. A pharmaceutical composition according to Claim 14 wherein said lubricants are selected from the group consisting of glyceryl behapate, stearates, stearic acid, hydrogenated vegetable oils, talc, waxes, Stearowet, boric acid, sodium benzoate, sodium acetate, sodium chloride, DL-Leucine, polyethylene glycols, sodium oleate, sodium lauryl sulfate, and magnesium lauryl sulfate.

16. A pharmaceutical composition according to Claim 14 wherein said lubricant comprises magnesium stearate.
17. A pharmaceutical composition according to Claim 1 wherein celecoxib is present in the range of about 25% to about 85% of the total weight of the composition.
18. A pharmaceutical composition according to Claim 1 further comprising one or more carrier materials selected from the group consisting of pharmaceutically acceptable diluents, disintegrants, wetting agents, and lubricants.
19. A pharmaceutical composition according to Claim 1 further comprising:
 - one or more pharmaceutically acceptable diluents, wherein said diluent or diluents are present in the range of about 10% to about 85% of the total weight of the composition; and
 - 5 one or more pharmaceutically acceptable disintegrants, wherein said disintegrants are present in the range of about 0.2% to about 10% of the total weight of the composition; and
 - wherein polyvinylpyrrolidone is present in the range of about 0.5% to about 10% of the total weight of the composition.
20. A pharmaceutical composition according to Claim 19 comprising one or more pharmaceutically acceptable wetting agents, wherein said wetting agents or wetting agents are present in the range of about 0.4% to about 10% of the total weight of the composition.
21. A pharmaceutical composition according to Claim 19 comprising one or more pharmaceutically acceptable lubricants, wherein said lubricant or lubricants are present in the range of about 0.2% to about 8% of the total weight of the composition.
22. A pharmaceutical composition according to Claim 19 comprising lactose.

23. A pharmaceutical composition according to Claim 19 comprising croscarmellose sodium.
24. A pharmaceutical composition according to Claim 19 comprising sodium lauryl sulfate.
25. A pharmaceutical composition according to Claim 19 comprising magnesium stearate
26. A pharmaceutical composition according to Claim 19 comprising microcrystalline cellulose.
27. A pharmaceutical composition according to Claim 1 comprising:
about 1 to about 95 weight percent of celecoxib;
about 5 to about 99 weight percent of lactose;
about 2 to about 10 weight percent of croscarmellose sodium; and
about 0.5 to about 10 weight percent of polyvinylpyrrolidone.
28. A pharmaceutical composition according to Claim 27 comprising about 0.25 to about 7 weight percent of sodium lauryl sulfate.
29. A pharmaceutical composition according to Claim 27 comprising about 0.25 to about 5 weight percent of magnesium stearate.
30. A pharmaceutical composition according to Claim 27 comprising about 5 to about 99 weight percent of microcrystalline cellulose.
31. A pharmaceutical composition according to Claim 1 comprising:
about 25 to about 85 weight percent of celecoxib;
about 5 to about 70 weight percent of lactose;
about 0.5 to about 10 weight percent of polyvinylpyrrolidone;
about 0.2 to about 6 weight percent of croscarmellose sodium;
about 0.4 to about 6 weight percent of sodium lauryl sulfate; and

about 0.2 to about 8 weight percent of magnesium stearate.

- 5 32. A pharmaceutical composition according to Claim 1 comprising:
about 27 to about 47 weight percent of celecoxib;
about 45 to about 65 weight percent of lactose;
about 0.5 to about 5 weight percent of polyvinylpyrrolidone; and
about 0.5 to about 5 weight percent of croscarmellose sodium.
- 5 33. A pharmaceutical composition according to Claim 1 comprising:
about 32 to about 42 weight percent of celecoxib;
about 50 to about 60 weight percent of lactose;
about 0.5 to about 3 weight percent of croscarmellose sodium;
about 1 to about 5 weight percent of polyvinylpyrrolidone; and
about 0.4 to about 6 weight percent of sodium lauryl sulfate.
- 5 34. A pharmaceutical composition according to Claim 1 comprising:
about 35 to about 39 weight percent of celecoxib;
about 54 to about 57 weight percent of lactose;
about 0.5 to about 2 weight percent of croscarmellose sodium;
about 1.5 to about 4.5 weight percent of polyvinylpyrrolidone;
about 2 to about 4 weight percent of sodium lauryl sulfate; and
about 0.5 to about 2 weight percent of magnesium stearate.
- 5 35. A pharmaceutical composition according to Claim 1 comprising:
about 65 to about 85 weight percent of celecoxib;
about 8 to about 28 weight percent of lactose;
about 0.5 to about 5 weight percent of polyvinylpyrrolidone; and
about 0.5 to about 5 weight percent of croscarmellose sodium.
- 5 36. A pharmaceutical composition according to Claim 1 comprising:
about 69 to about 79 weight percent of celecoxib;
about 13.5 to about 23.5 weight percent of lactose;
about 0.5 to about 3 weight percent of croscarmellose sodium;
about 1 to about 5 weight percent of polyvinylpyrrolidone; and

about 0.4 to about 6 weight percent of sodium lauryl sulfate.

5 37. A pharmaceutical composition according to Claim 1 comprising:
about 72 to about 76 weight percent of celecoxib;
about 16.5 to about 20.5 weight percent of lactose;
about 0.5 to about 2 weight percent of croscarmellose sodium;
about 1.5 to about 4.5 weight percent of polyvinylpyrrolidone;
about 2 to about 4 weight percent of sodium lauryl sulfate; and
about 0.5 to about 2 weight percent of magnesium stearate.

5 38. A pharmaceutical composition according to Claim 1 comprising:
about 30 to about 50 weight percent of celecoxib;
about 30 to about 50 weight percent of lactose;
about 0.5 to about 10 weight percent of croscarmellose sodium; and
about 0.5 to about 5 weight percent of polyvinylpyrrolidone.

5 39. A pharmaceutical composition according to Claim 1 comprising:
about 35 to about 45 weight percent of celecoxib;
about 35 to about 45 weight percent of lactose;
about 1 to about 5 weight percent of croscarmellose sodium;
about 1 to about 5 weight percent of polyvinylpyrrolidone; and
about 5 to about 15 weight percent of microcrystalline cellulose.

5 40. A pharmaceutical composition according to Claim 1 comprising:
about 38 to about 42 weight percent of celecoxib;
about 38 to about 42 weight percent of lactose;
about 1.5 to about 4.5 weight percent of croscarmellose sodium;
about 1.5 to about 4.5 weight percent of polyvinylpyrrolidone;
about 8 to about 12 weight percent of microcrystalline cellulose;
about 2 to about 4 weight percent of sodium lauryl sulfate; and
about 0.5 to about 2 weight percent of magnesium stearate.

41. A pharmaceutical composition according to Claim 1 comprising:
about 80 to about 220 mg of celecoxib;

about 30 to about 225 mg of lactose;
about 0.5 to about 25 mg of polyvinylpyrrolidone; and
5 about 0.5 to about 25 mg of croscarmellose sodium.

42. A pharmaceutical composition according to Claim 41 comprising about 0.5 to about 25 mg of sodium lauryl sulfate.

43. A pharmaceutical composition according to Claim 41 comprising about 0.2 to about 10 mg of magnesium stearate.

44. A pharmaceutical composition according to Claim 41 comprising about 1 mg to about 70 mg of microcrystalline cellulose.

45. A pharmaceutical composition according to Claim 1 in the form of a capsule comprising:

about 100 mg of celecoxib;
about 149.75 mg of lactose monohydrate;
5 about 8.1 mg of sodium lauryl sulfate;
about 6.75 mg of polyvinylpyrrolidone;
about 2.7 mg of croscarmellose sodium; and
about 2.7 mg of magnesium stearate.

46. A pharmaceutical composition according to Claim 1 in the form of a capsule comprising:

about 200 mg of celecoxib;
about 49.75 mg of lactose monohydrate;
5 about 8.1 mg of sodium lauryl sulfate;
about 6.75 mg of polyvinylpyrrolidone;
about 2.7 mg of croscarmellose sodium; and
about 2.7 mg of magnesium stearate.

47. A pharmaceutical composition according to Claim 1 in the form of a tablet comprising:
about 100 mg of celecoxib;

5 about 101.88 mg of lactose monohydrate;
about 7.5 mg of sodium lauryl sulfate;
about 6.25 mg of polyvinylpyrrolidone;
about 7.5 mg of croscarmellose sodium;
about 1.88 mg of magnesium stearate; and
about 25 mg of microcrystalline cellulose.

48. A pharmaceutical composition according to Claim 1 in the form of a
tablet comprising:
5 about 200 mg of celecoxib;
about 203.8 mg of lactose monohydrate;
about 15 mg of sodium lauryl sulfate;
about 12.5 mg of polyvinylpyrrolidone;
about 15 mg of croscarmellose sodium;
about 3.75 mg of magnesium stearate; and
about 50 mg of microcrystalline cellulose.
49. A pharmaceutical composition according to Claim 1 comprising celecoxib,
polyvinylpyrrolidone, lactose, sodium lauryl sulfate, croscarmellose sodium,
and magnesium stearate.
50. A pharmaceutical composition according to Claim 1 in a unit oral dosage
form.
51. A pharmaceutical composition according to Claim 1, wherein said
composition is in the form of a unit dosage tablet or capsule.
52. A pharmaceutical composition according to Claim 1, wherein said
composition is in the form of a unit dosage capsule.
53. A pharmaceutical composition according to Claim 1 in the form of an oral unit
dosage tablet or capsule having a 100 mg or 200 mg dose of celecoxib.

54. A pharmaceutical composition comprising celecoxib, wherein said composition is suitable for once or twice a day oral administration for the treatment or prophylaxis of cyclooxygenase-2 mediated conditions and disorders.
55. A pharmaceutical composition according to Claim 54 comprising polyvinylpyrrolidone and croscarmellose sodium.
56. A pharmaceutical composition according to Claim 54 comprising lactose.
57. A pharmaceutical composition according to Claim 54 comprising sodium lauryl sulfate.
58. A pharmaceutical composition according to Claim 54 comprising magnesium stearate.
59. A pharmaceutical composition according to Claim 54 comprising microcrystalline cellulose.
60. A pharmaceutical composition according to Claim 1 wherein said composition provides a therapeutic effect as a cyclooxygenase-2 inhibitor over an interval of about 12 to about 24 hours after ingestion.
61. A pharmaceutical composition according to Claim 60 wherein said composition provides a therapeutic effect as a cyclooxygenase-2 inhibitor over an interval of about 24 hours.
62. A pharmaceutical composition comprising celecoxib wherein at least 50% of the celecoxib in the composition is released in vitro within 15 minutes of ingestion of the composition.
63. A pharmaceutical composition according to Claim 62 in the form of an oral dosage tablet or capsule suitable for once or twice a day oral administration.

64. A pharmaceutical composition comprising celecoxib wherein said composition provides an average blood serum concentration of celecoxib of at least 100 ng/mL over an interval of about 24 hours after ingestion.
65. A unit oral dosage form of the pharmaceutical composition of Claim 1 wherein the composition is directly encapsulated or directly compressed into tablets.
66. A unit oral dosage form of the pharmaceutical composition of Claim 1 wherein the composition is wet granulated prior to encapsulation or compression into tablets.
67. A unit oral dosage form of the pharmaceutical composition of Claim 1 wherein the composition is dry granulated prior to encapsulation or compression into tablets.
68. The pharmaceutical composition of Claim 1 wherein at least 90% of the celecoxib particles used in the preparation of the composition are less than about 100 microns in size.
69. A method of treating a condition or disorder where treatment with a cyclooxygenase-2 inhibitor is indicated, comprising orally administering a composition according to Claim 1 once or twice a day to a patient in need of such treatment.
70. A method of treating a condition or disorder where treatment with a cyclooxygenase-2 inhibitor is indicated, comprising orally administering a composition according to Claim 19 once or twice a day to a patient in need of such treatment.
71. A method of treating a condition or disorder where treatment with a cyclooxygenase-2 inhibitor is indicated, comprising orally administering a composition according to Claim 27 once or twice a day to a patient in need of such treatment.

72. A method according to Claim 69 wherein the condition or disorder is rheumatoid arthritis.
73. A method according to Claim 69 wherein the condition or disorder is osteoarthritis.
74. A method of preparing a pharmaceutical composition comprising:
 wet granulating celecoxib and one or more carrier materials to form a wet granulated mixture; and
 preparing an oral dosage form of the pharmaceutical composition from the wet granulated mixture.
75. The method of claim 74 wherein each unit dosage comprises celecoxib in an amount from about 100 mg to about 200 mg.
76. The use of celecoxib in the manufacture of a medicament for the treatment or prophylaxis of cyclooxygenase-2 mediated conditions and disorders.
77. A method according to Claim 76 wherein the condition or disorder is rheumatoid arthritis.
78. A method according to Claim 76 wherein the condition or disorder is osteoarthritis.

Abstract of the Disclosure

5 The invention relates to oral pharmaceutical compositions useful in the treatment of cyclooxygenase-2 mediated conditions and/or disorders comprising the active agent celecoxib in an amount from about 10 mg to about 1000 mg and one or more carrier materials.